

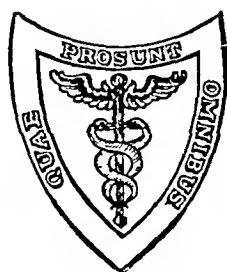
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E. B. KRUMBHAAR, M.D.
EDITOR

WILLIAM C. STADIE, M.D.
ACTING ASSISTANT EDITOR

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THE
AMERICAN JOURNAL
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JANUARY, 1943

ORIGINAL ARTICLES

THE ADMINISTRATION OF SULFONAMIDE MICRO-CRYSTALS
BY INHALATION*

BY T. N. HARRIS, M.D.

HARRIET E. SOMMER

AND

CHARLES C. CHAPPLE, M.D.

PHILADELPHIA, PA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania,
and the Children's Hospital of Philadelphia)

THE usefulness of the sulfonamides has been limited by their low solubility in water. For parenteral administration the water solubility is so low that an effective dose of the drug requires large volumes of solution. The sodium salts of the sulfonamides, on the other hand, are more soluble in water, but their extreme alkalinity limits their use in parenteral injection or application to mucous membranes.⁴ There are some exceptions to these limits of usefulness,^{3,5,6} but any form of the drugs which could increase their possible modes of administration would obviously be valuable.

Recently Chambers and his associates² developed a method for producing aqueous preparations of the sulfonamides which are neutral in reaction, yet adequately concentrated. They prepared minute crystals, "micro-crystals," of these drugs, which form a stable aqueous suspension resembling milk of magnesia in physical properties. This preparation can be injected through fine hypodermic needles, poured into the interstices of wounds or sprayed to form a sulfonamide "fog" in the air. Experiments on the use of this micro-crystal suspension in wounds have been reported elsewhere.¹ This paper is concerned with the administration of sulfonamides by inhalation, by introducing sulfonamide smoke into the air.

* Aided by a grant from the Smith, Kline & French Laboratories, Philadelphia.

Method. The sulfathiazole "smoke" used in these experiments was derived from a 5% aqueous suspension of sulfathiazole micro-crystals.* The suspension was introduced into an atomizer supplied with compressed air which produced a finely divided spray. The resultant spray was led into a chamber containing Swiss white mice weighing about 20 gm. In this chamber the droplets quickly dried, leaving the sulfathiazole "smoke" in the air. Most of the particles of sulfathiazole in air were about 1.6 to 4.8 micra in diameter. Larger crystals were also found.

Pharmacologic Experiments. A number of experiments were performed to determine the effect on normal mice of prolonged inhalation of such "smoke." Groups of mice were placed for different lengths of time in a chamber containing the sulfathiazole smoke and were examined at various intervals thereafter.

The mice were examined for general ill effects and for any gross changes in the lungs. Analyses for sulfonamide concentration in the blood and for total sulfonamide content of the lungs and stomach were carried out.

TABLE 1.—THE SULFONAMIDE CONCENTRATION OR CONTENT IN BLOOD, LUNG AND STOMACH AFTER INHALATION OF SULFATHIAZOLE SMOKE

Length of exposure	Time after end of exposure	Blood, mg./100 cc.	Lung contents, mg.	Stomach contents, mg.
15 min.	0	1 91	0 0033	
	0	1 45	0 0027	0 055
30 min.	0	5 87	0 0086	0 037
	0	3 17	0 0049	
30 min.	30 min.	1 98	0 0030	
	30 min.	3 56	0 0037	
30 min.	1 hour	2 19	0 0027	
	1 hour	2 11	0 0027	
1 hour	0	2 38	0 0086	0 223
	0	5 08	0 0093	0 180
1 hour	1 hour	3 50	0 0046	
	1 hour	2 90	0 0030	
1 hour	1 hour	1 03	0 0063	
	4 hours	1 25	0 0010	
1 hour	8 hours	1 65		
	8 hours	1 58		
2 hours	0	2 97	0 0066	
	0	1 65	0	
2 hours	1 hour	1 78	0 0037	
	1 hour	4 88	0 0073	
2 hours	2 hours	7 00	0 0076	
	2 hours	3 89	0 0053	
2 hours	4 hours	2 11	0 0040	
	4 hours	6 79	0 0033	
4 hours	0	15 18		
	0	11 55		
4 hours	1 hour	16 57		
	1 hour	13 27		
4 hours	2 hours	1 09		
	2 hours	5 21		
4 hours	4 hours	2 81		
	4 hours	2 05		
4 hours	8 hours	0 59		0 286
	8 hours	1 98		

* This material was supplied by the Smith, Kline & French Laboratories, Philadelphia.

No general ill effects were observed in the mice during or after the inhalation of the sulfathiazole smoke and gross examination of the lungs at different intervals up to several days after the inhalation revealed no changes except for mild hyperemia soon after the inhalation.

Typical results of the analyses for sulfonamide are shown in Table 1.

In order to determine whether significant amounts of sulfathiazole can be absorbed from the lungs, tracheotomy and ligation of the esophagus were performed on guinea pigs and the tracheotomy tube was exposed to the spray. Control guinea pigs were exposed to sulfathiazole spray in a chamber. The results of this experiment are shown in Table 2.

TABLE 2.—BLOOD SULFATHIAZOLE CONCENTRATIONS IN NORMAL AND TRACHEOTOMIZED GUINEA PIGS

Tracheotomized	Normal
Pig 1.—3.46 mg./100 cc. -	3 89 mg./100 cc.
Pig 2.—1.93 mg./100 cc.	

Finally, to indicate whether the blood levels attained in normal mice exposed to the smoke were due primarily to pulmonary or gastro-intestinal absorption, sulfathiazole was administered by gavage to normal mice and its effect on the blood level determined. It was found that 10 mg. of sulfathiazole placed in the stomach gave rise to a blood concentration of 12–13 mg./100 cc.; and 5 mg. in the stomach, to a maximum level of 4–5 mg./100 cc. Amounts of sulfathiazole such as those found in the stomachs of our mice could not then be considered of major importance in the blood levels observed since the gastric contents never exceeded 0.25 mg. following inhalation of the smoke.

As a control on the particular usefulness of the micro-crystals for sulfathiazole inhalation, mice were exposed to a spray of sodium sulfathiazole solution under similar circumstances. All these mice died within a few hours, their lungs showing grossly an extreme hyperemia.

Chemotherapeutic Experiments. An interesting and possibly important direction for testing the particular value of the inhalation route of administration of the drug was indicated by the experiments of Wells and Henle.⁷

It is known that mice are strongly resistant to inhaled pneumococci, and can breathe air heavily contaminated with these bacteria without ill effects. These authors found, however, that if mice had previously inhaled sublethal doses of influenza virus they would become more susceptible to inhaled pneumococci, and would often develop fatal pneumonia.

If this could be interpreted as a decrease in resistance of the lung to pneumococci, then one could suspect an analogy to a number

of situations in human medicine. An increase in likelihood of secondary bacterial pneumonia complicates a number of important infections and toxic states.

Accordingly, experiments were undertaken to evaluate the effectiveness of sulfathiazole smoke in secondary bacterial pneumonia of mice. Preliminary experiments were done to determine the optimal relations among the factors involved. It was found that a spray of a 1:500 dilution of influenza A virus egg fluid (Strain P2) was barely sublethal. Moreover, if mice exposed to this spray were exposed to a spray of pneumococcus broth culture 6 days later, 70 to 80% of them would die of pneumonia in a few days. Normal mice showed no ill effects from exposure to the same spray of pneumococci.

These factors were optimal in that they produced the most striking difference in mortality rate between normal mice and mice previously exposed to air-borne influenza virus; *i. e.*, the most striking evidence of decreased resistance to air-borne pneumococci. Experiments were then carried out to determine whether the smoke of micro-sulfathiazole could prevent the secondary bacterial invasion in mice following a primary sublethal infection with the influenza virus. Exposure to the sulfathiazole smoke lasted 2 to 3 hours, 4 times a day for 3 days starting with a period 2 hours prior to inhalation of the pneumococci. Six days after exposure to the pneumococci, the mice were sacrificed, the lungs examined grossly and lungs and heart's blood subcultured and examined for pneumococci. Table 3 illustrates the results from a typical experiment.

It is, of course, known that orally-administered sulfathiazole

TABLE 3.—THE EFFECT OF SULFATHIAZOLE INHALATION ON INFLUENZAL MICE EXPOSED TO PNEUMOCOCCI.

	Observations on each mouse; groups of 10									
	1	2	3	4	5	6	7	8	9	10
Influenza virus alone . . .	D13 (x)	D13 (4)	(1)	(1)	0	0	0	0	0	0
Pneumococcus control . . .	0	0	0	0	0	0	0	0	0	0
Influenza virus + pneumococcus	D9* (4)	D9* (4)	D9* (4)	D9* (3)	D9* (3)	D9* (3)	D10 (x)	D11* (4)	0	0
Influenza virus + pneumococcus + sulfathiazole inhalation . .	D11* (4)	(4)	(3)	(3)	0	0	0	0	0	0

D9, died on 9th day, etc. (1), (2), (3), (4) indicate severity of lung lesions. (x), could not be examined. 0, no lesion.

* Pneumococcus Type I recovered from lungs and/or heart's blood.

TABLE 4.—THE EFFECT OF SULFATHIAZOLE ADMINISTERED BY GASTRIC GAVAGE ON INFLUENZAL MICE EXPOSED TO PNEUMOCOCCI

	Observations on each mouse, groups of 10									
	1	2	3	4	5	6	7	8	9	10
Influenza virus control . . .	(3)	(3)	(3)	(2)	(2)	(2)	(2)	0	0	0
Pneumococcus control . . .	0	0	0	0	0	0	0	0	0	0
Influenza virus + pneumococcus	D9*	D10*	D10*	D11*	D12*	D12*	D12*	(3) ²	(2) ²	0
Influenza virus + pneumococcus + sulfathiazole gavage . . .	(3)	(3)	(3)	(2)	(2)	(2)	(1)	(1)	0	0

D1, died on 1st day, etc. (1), (2), (3), (4) indicate severity of lung lesions. (x), could not be examined. 0, no lesion. (1) and (2) indicate severity of lung lesions.

* Pneumococcus Type I recovered from lungs and/or heart's blood.

can markedly reduce the mortality of pneumonia, and as a control we repeated the experiment shown in Table 3 substituting gastric gavage of micro-sulfathiazole suspension for the inhalation. It was found that this secondary pneumonia could be successfully treated with oral sulfathiazole, provided a sufficiently high blood-level were maintained. The results of such an experiment are shown in Table 4.

Discussion. The pharmacologic experiments show that sulfathiazole can be administered by inhalation and that high blood levels can be attained in this manner. There is also considerable evidence that the blood concentration is due to absorption from the lung rather than from the stomach.

The very low amounts of drug found in the lung are of interest, since they indicate a very rapid solution into the blood stream of the crystals inhaled in the smoke. The mild hyperemia and the rather quick rise in blood level during the first hour of exposure are consistent with this interpretation. The presence of minute crystals of drug may well be a sufficient irritant to stimulate such hyperemia.

Wide differences are found between the blood levels of different mice exposed under presumably similar conditions, but these are very probably due to technical difficulties. First, the chambers used thus far have been small ones without circulating devices, and the air stream from the spray is fairly forceful (15 to 26 pounds per square inch). These mechanical factors probably produce great differences in air-concentration of the drug throughout the chamber. Secondly, the mice tend to collect in heaps, partly to avoid the direct air stream. The fur of uppermost mice probably filters out some of the drug from the air to be inhaled by those below. Work is under way now to resolve these technical difficulties.

The chemotherapeutic results are at the present writing very stimulating. We have shown that the inhalation of sulfathiazole smoke can strikingly reduce the mortality of secondary pneumonia induced by a state of decreased resistance to the pneumococcus. There is some reason to suspect that the amounts of drug administered were a good deal higher than the threshold value. However, a sufficiently high blood concentration of sulfathiazole attained by other means can accomplish the same result.

In the purely therapeutic sense, then, no qualitative superiority of the pulmonary over the oral route has been demonstrated thus far, and any quantitative difference is yet to be investigated.

As to possible prophylactic effects, however, the investigation of any qualitative difference between the two modes of administration seems well worth while. With respect to practical applications to human medicine* it would be well to know whether either method

* Dr. Chapple has kindly made us a simple insufflator, operated with an atomizer bulb, which easily introduces the dry micro-crystals as "smoke" into nasal or oral cavities in sufficient amounts to affect rhinitis or pharyngitis locally as well as producing satisfactory sulfonamide blood levels. We hope that he will report on this aspect shortly.—ED.

can prevent pneumonia to the exclusion of the other method, since prevention is, of course, far preferable to any decrease of mortality of pneumonia itself. And theoretically, it would be of interest to determine whether direct application of sulfathiazole to the lung can increase its effective resistance by any local mechanism.

Summary. A technique is described for producing a "smoke" of sulfonamides in air by spraying a suspension of minute crystals.

Mice inhaling sulfonamide smoke develop high blood concentrations of the drug.

This method of administration can be used to reduce greatly the mortality due to inhalation of pneumococcus in mice suffering with influenza.

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MEDICATION BY CHEWING SULFADIAZINE AND OTHER DRUGS INCORPORATED IN A PARAFFIN BASE

A PRELIMINARY REPORT

By JOHN H. ARNETT, M.D.

ASSOCIATE PROFESSOR OF MEDICINE, GRADUATE SCHOOL, UNIVERSITY OF PENNSYLVANIA
CHIEF OF MEDICAL SERVICE "D," EPISCOPAL HOSPITAL
PHILADELPHIA, PA.

(From the Medical Service and the Laboratory of Chemistry of the Episcopal Hospital)

The incorporation of acetylsalicylic acid, pepsin, phenolphthalein and flavoring agents in chewing gum is too well known to require comment. Paraffin, on the other hand, has not, as far as I have been able to determine, been employed in this manner; though the chewing of pure paraffin to promote salivary secretion has been recommended in the treatment of bleeding peptic ulcer. If drugs incorporated in paraffin are slowly released in the saliva when chewed and if, in the process of chewing and swallowing, they come into intimate contact with the gums, pharynx and esophagus, possibilities for more effective treatment of gingivitis, stomatitis, pharyngitis, and esophagitis by this means may be opened. The present study suggests that such is the case.

Fifteen milligrams ($\frac{1}{4}$ gr.) of gentian violet and later 0.3 gm. (5 gr.) of methylene blue were incorporated with 1 gm. (15 gr.) of paraffin* and were given to 13 subjects to chew. Observations as to the extent and degree of mucosal staining were made by Drs. O. C. Hirst and J. A. Bertolet, chiefs of services at the Episcopal Hospital.

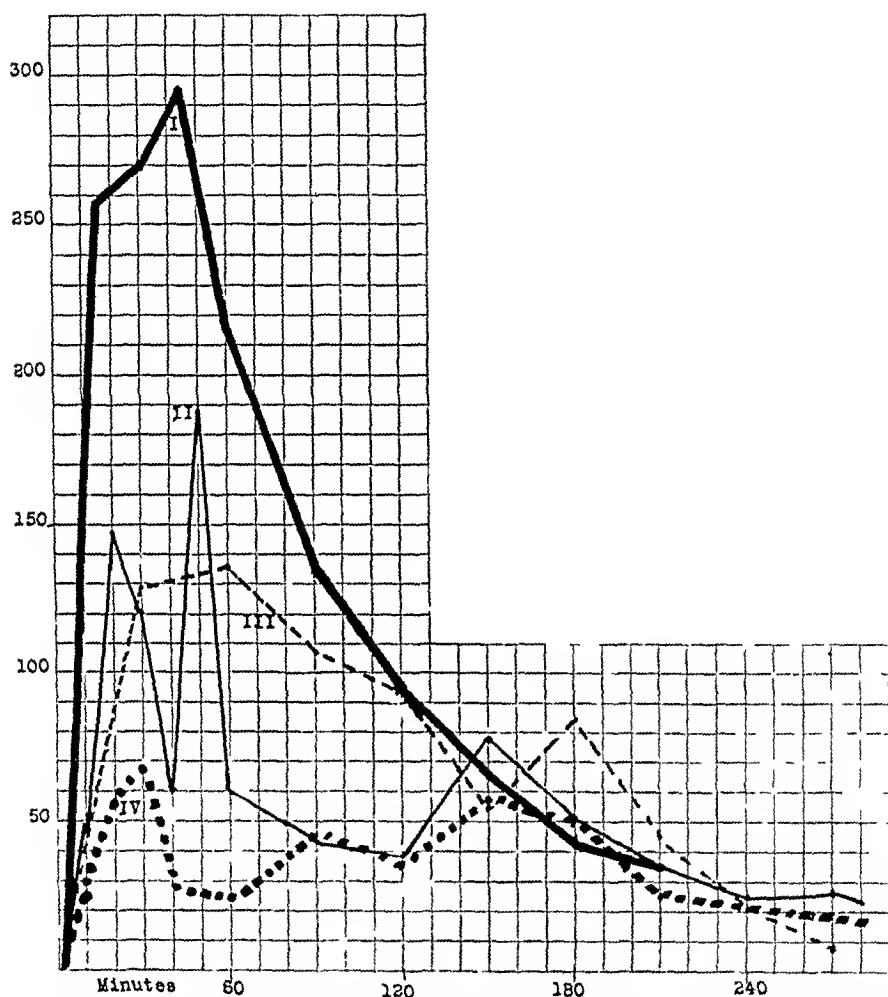


CHART 1.—Level of sulfadiazine in saliva during chewing of 0.3 gm. of the drug incorporated in 1 gm. of paraffin in 4 cases. Blood sulfadiazine levels at the end of Cases 2 and 4, respectively, were 1.2 mg. and less than 0.8 mg. per 100 cc.

Results. It was found that the dyes stained the tongue and gingival margins deeply; that next in intensity the remaining buccal

* Paraffin having a melting-point of 50° to 52° C., such as is used in embedding pathologic material, is used in cold weather; ordinary paraffin such as is sold at grocery stores for putting up jellies is satisfactory only in summer. In either case the paraffin should be warmed in the mouth before being chewed.

The sulfadiazine paraffin cubes, at present used by me, are furnished through the kindness of Lederle Laboratories, Inc., Pearl River, N. Y.

mucosa was stained; that the degree and extent of staining of the mucous membrane back of the anterior pillars and soft palate depended largely upon the position assumed by the patient while chewing and swallowing. The tonsils and posterior pharynx were usually not stained if the patient assumed the upright position during the experiment; but with the subject chewing and swallowing in the recumbent position with the head lower than the shoulders, the tonsils and posterior pharynx usually became definitely stained. The stained area varied, but in no case did the dye reach to the true vocal cords, the eustachian tube orifices or the sphenoid-ethmoidal area. Usually it was limited to the structures in close proximity to the oral cavity, including the tonsils and posterior pharyngeal wall. This was interpreted as indicating the possibility of securing maximum local action upon the gums, tongue and buccal mucosa, and action to a lesser degree upon the oropharynx from the chewing of medicated paraffin. Action upon the esophagus was taken for granted.

The next step involved the matter of dosage. Eleven subjects were given paraffin containing from 0.065 gm. (1 gr.) to 0.3 gm. (5 gr.) of sulfadiazine to chew, and serial salivary sulfadiazine determinations were made by Miss N. M. Catena, B.S., M.T. (A.S.C.P.). It was found that 0.3 gm. (5 gr.) of the drug was the most satisfactory amount to incorporate in the paraffin. Four of the resulting curves are shown in Chart 1. It will be seen that salivary sulfadiazine levels ranging from 33 to 96 mg. per 100 cc. of saliva (average, 66.5 mg.) result from chewing this dose for 2 hours. At the end of 3 hours the levels ranged from 42 to 84 mg. per 100 cc. of saliva (average, 56.7 mg.). Considering the fact that sulfadiazine blood levels of between 5 and 15 mg. per 100 cc. of blood are generally regarded as satisfactory in the treatment of pneumonia and that levels of 20 to 25 mg. per 100 cc. were found after 4 hours in the saliva, it was thought that the above salivary levels were sufficiently high to be useful locally. The findings indicate that a therapeutic trial of the drug in this dosage is justified, the medicated paraffin sticks being given to patients with directions to chew until the next meal and then discard. Two or three chews per minute is sufficient. The material is left in the mouth throughout the night. The paraffin is, of course, quite harmless if swallowed. This method of treatment is being tried on a series of cases of tonsillitis and pharyngitis, the results to be reported in a later paper. Neosarsphenamine incorporated in paraffin has also been used in the treatment of Vincent's infection of the gums and tonsils, and sodium bicarbonate incorporated in paraffin in the treatment of pyrosis.

Summary. The incorporation of various drugs in a paraffin base to be chewed offers a means of prolonged medication of the mouth, pharynx and upper gastro-intestinal tract.

THE EFFECT OF IRON ON THE HEMOGLOBIN REGENERATION IN BLOOD DONORS

BY ADELAIDE P. BARER, PH.D.

RESEARCH ASSISTANT

AND

WILLIS M. FOWLER, M.D.

ASSOCIATE PROFESSOR OF MEDICINE

IOWA CITY, IOWA

(From the Department of Internal Medicine, State University of Iowa, College of Medicine)

THE present great demand for donors to supply blood and serum for transfusions makes it important to know how rapidly the hemoglobin returns to its normal level, how frequently blood may be taken from an individual with safety, and the advisability of therapy to hasten hemoglobin regeneration. A majority of the previous reports on this subject have only shown that professional donors are able to give repeated donations within a space of a few months without developing anemia. Snapper, Liu, Chung and Yu⁸ reporting on a group of Chinese donors found that hypochromic anemia occasionally developed in those who subsisted on an inadequate diet and that the administration of iron aided in alleviating their anemia. Santy⁷ also has shown that ferrous sulfate increased the rate of hemoglobin regeneration in 27 blood donors to whom it was administered. With 12 gr. of ferrous sulfate per day, he found the regeneration to be 8 times as fast as without iron and concluded that it was best to begin the administration of iron before the blood donation was made so as to build up an iron reserve to compensate for the expected blood loss.

In a previous communication⁴ we presented some of the data acquired from a study of 200 blood donors who had given a total of 636 donations and showed that the average time required for the hemoglobin to return to its original level was 49.6 days when 500 to 600 cc. of blood was withdrawn, and that hemoglobin was regenerated at a rate of 0.0495 gm. per 100 cc. of blood per day under these circumstances. A majority of the subjects, 74.2%, had returned to their original hemoglobin level at the end of 8 weeks, but 25.8% required a longer recovery period, up to 15 weeks. When an iron salt was administered to a group of 89 of these donors after their second blood donation it was found that the rate of hemoglobin regeneration was increased by 49% so that the average daily hemoglobin increase per 100 cc. of blood was 0.0772 gm. and the recovery period was shortened to 35.2 days. Under these conditions it was found that 93.5 of the subjects had regained their normal hemoglobin level at the end of 8 weeks. Iron therapy was administered continuously and some of these subjects gave as many as 5 dona-

tions, subsequent donations being given as soon as their normal hemoglobin level had been reached. It was found that in spite of the continuous iron therapy there was a gradual decline in the rate of hemoglobin formation after each donation until it was being formed at a rate which was no more rapid than it had been without iron therapy. It seemed, therefore, as if iron had progressively less effect with its continuous administration. In Table 1 is shown the decline in the average daily hemoglobin regeneration in these subjects after repeated donations. If iron were acting only to replace an iron deficiency it would seem that its effect should remain constant, since previous work¹ has shown that the dose of iron which was administered (iron and ammonium citrates 1 gm. per day) is sufficiently large to be effective in iron deficiency anemias. Balance studies⁵ have shown that from this amount of iron and ammonium citrates 53.7 mg. of iron per day are retained in the body, whereas the regeneration of 0.0772 gm. of hemoglobin per 100 cc. of blood per day would require only 12.9 mg. of iron in an individual with a blood volume of 5000 cc. The size of the dose would not appear to be a factor in the gradual lessening in the hemoglobin response.

TABLE 1.—AVERAGE DAILY HEMOGLOBIN REGENERATION WITH AND WITHOUT IRON THERAPY

(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases				
		155	83	31	12	11
1	No therapy	.050	.052	.055	.055	.055
2	Continuous iron therapy	..	.077	.087	.101	.101
3	Continuous iron therapy069	.072	.071
4	Continuous iron therapy049	.049
5	Continuous iron therapy058

Iron was administered to groups of these blood donors in alternating periods with therapy interspersed with recovery periods during which no medication was given. The subjects for this investigation were predominantly medical students, the resident staff, and hospital employees and the data presented here are exclusively on male donors. Hemoglobin and hematocrit determinations were made before the blood donation, 24 hours after the donation and at weekly intervals thereafter until the blood hemoglobin had returned to its normal level. From these data were determined the length of time required for the hemoglobin to return to normal, the weekly gain in hemoglobin, and the average daily hemoglobin increase per 100 cc. of blood. The methods and procedures employed were the same as described in the previous communication.⁴

In Table 2 is shown the average daily hemoglobin regeneration in 2 groups of subjects. In the first group are the results in 4 subjects who gave 1 blood donation without iron therapy and 6 subsequent

donations while receiving continuous iron therapy. The second group shows the results in 2 subjects who gave 9 subsequent donations while receiving therapy. It will be noted that there is a marked increase in the rate of hemoglobin formation during the first recovery period on iron therapy but a gradual decline thereafter except for a secondary increase during the 5th period on iron therapy which is again followed by a slowing in the rate of regeneration.

TABLE 2.—AVERAGE DAILY HEMOGLOBIN REGENERATION
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases	
		4	2
1	No therapy	051	045
2	Continuous iron therapy	123	113
3	Continuous iron therapy	059	064
4	Continuous iron therapy	059	059
5	Continuous iron therapy	044	053
6	Continuous iron therapy	093	105
7	Continuous iron therapy	043	056
8	Continuous iron therapy		046
9	Continuous iron therapy		054
10	Continuous iron therapy		076

TABLE 3.—INDIVIDUAL RECORDS OF AVERAGE DAILY HEMOGLOBIN REGENERATION
(Gm. hemoglobin per 100 cc. blood per day)

Donation		Subject					
		1	2	3	4	5	6
1	No therapy	058	072	044	072	030	059
2	Continuous iron therapy	130	134	140	123	129	098
3	Continuous iron therapy	114	044	044	064	059	068
4	Continuous iron therapy	094	025	061	058	079	039
5	Continuous iron therapy	043	134	034	038	043	062
6	Continuous iron therapy	035	042	088	076	161	048
7	Continuous iron therapy			033	029	065	046
8	Continuous iron therapy					048	043
9	Continuous iron therapy					040	069
10	Continuous iron therapy					084	068
11	Continuous iron therapy						063
12	Continuous iron therapy						090
13	Continuous iron therapy						028
14	Continuous iron therapy						041
15	Continuous iron therapy						157

The same feature is brought out in Table 3 in which are presented individual records of 6 subjects who were similarly treated with the continuous administration of iron after recovery from the first blood donation. In each instance the first period on iron therapy is characterized by a marked increase in the rate of hemoglobin regeneration but a slower rate prevails after subsequent donations. There is, in individual cases, considerable variation from one period to another but except for Case 1 each shows at least one subsequent period in which there is a definite secondary increase in hemoglobin regeneration. This appears during the 4th or 5th period on iron therapy in Cases 2, 3, 4, and 5, while in Case 6 there is an accelerated regeneration in the 11th and 14th periods while on iron therapy.

It is impossible to say whether or not the iron therapy is responsible for this acceleration in the later periods. In cases which were followed through 4 postdonation periods without iron therapy there was a moderate increase in hemoglobin formation in the 4th period but the change was not marked. From these data there is no evidence of a permanent lessening of the hemoglobin regenerative power as the rate of production does not drop significantly or consistently below the rate which prevailed before iron therapy was begun so that repeated donations of blood may be made without evident harm to the individual as far as hemoglobin formation is concerned. It is also apparent that iron therapy does not exert a sustained effect on hemoglobin regeneration.

TABLE 4.—AVERAGE DAILY HEMOGLOBIN INCREASE IN GROUPS RECEIVING AND NOT RECEIVING IRON THERAPY
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases			
		33	13	8	2
1	No therapy	.055	.054	.053	.061
2	Iron therapy	.073	.087	.088	.121
3	No therapy	.056	.061	.063	.070
4	Iron therapy	..	.079	.073	.072
5	No therapy065	.057
6	No therapy024

In Table 4 is shown the average daily hemoglobin increase in groups of donors to whom iron was administered after alternate donations and withheld after the others. It will be noted that the usual increased rate of hemoglobin formation was present during the first period of iron administration, but that the subsequent administration of iron, while causing an increase as compared to the preceding period, did not produce as great a response as was obtained with its first administration of iron. In those periods during which no medication was given it is seen that the rate of hemoglobin regeneration decreases as compared to the preceding periods with iron therapy, but it will be noted that the rate does not drop to the level of the first donation. It appears therefore that the effect of the iron previously administered is carried over into the subsequent period. This is the type of response that would be anticipated from previous studies on the effect of iron therapy on hemoglobin formation in which it was shown that there is a peak in the rate of hemoglobin regeneration which is followed by a decreased regenerative rate even though iron is administered continuously.³ Since the rate of hemoglobin regeneration during the periods without iron does not drop below the original control level it does not seem that the lessened effect of subsequent iron therapy can be explained on the basis of bone marrow exhaustion. It is rather on the basis of a lessened effect of iron itself on hemoglobin production.

In Table 5 are the results obtained in subjects who received no therapy after their first donation, iron therapy during 2 subsequent

postdonation periods and then no therapy after the following donations. In the 1st period of iron therapy a marked increase was noted; during the 2d period of iron therapy the response was less marked, and then with no therapy the rate of regeneration dropped markedly. This illustrates the fact that even with the giving of iron for a longer period of time and the storage of larger amounts of iron in the tissues during 2 periods of therapy there is still a sharp drop in the rate of hemoglobin regeneration when the medication is discontinued. Although adequate reserves are built up during the preceding periods of therapy, the regeneration of hemoglobin drops with the discontinuance of iron. This drop is no greater than occurred in the corresponding period shown in Table 1 when iron was given continuously so that the decreased rate cannot be laid directly to the withholding of iron. This comparable drop in the rate of hemoglobin regeneration which occurred in corresponding postdonation periods regardless of whether iron is given continuously (Table 1) or discontinued (Table 5) corresponds to the results obtained in mild anemia. To one group of anemias iron was given continuously and to a second group it was given for 60 days and then discontinued.³ The resultant curve of hemoglobin regeneration was similar in both groups and corresponds to the results observed in these blood donors.

TABLE 5.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases	
		7	4
1	No therapy	.047	.050
2	Iron therapy	.082	.092
3	Iron therapy	.069	.077
4	No therapy	.041	.047
5	Iron therapy	..	.059

It will also be noted in Table 5 that the subsequent administration of iron after one period without the medication failed to produce as great a response as was previously obtained. There is a slight response, however, which is more evident when compared to the results shown in Table 6 where iron was withheld for 2 periods. In Table 5, Period 5, iron was given, while in Table 6, Period 5, it was withheld. With iron therapy during this corresponding period there is a definite increase which is not true when iron was withheld.

In Table 7 the subjects received no iron for the first 2 periods during which the rate of regeneration remained about constant whereas with iron therapy in the 3d postdonation period the usual marked increase occurred. This is further evidence that the results are due to iron rather than to a stimulation resulting from the loss of blood, since in the previous tables iron was given in the 2d period and the rate of regeneration increased with this medication. In the present group, Period 2 was passed without medication and

without change in hemoglobin formation, whereas the giving of iron in Period 3 produced the expected increase. Withholding iron in Period 4 led to a prompt reduction in hemoglobin formation.

TABLE 6.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases	
		2	
1	No therapy	043	
2	Iron therapy	072	
3	Iron therapy	049	
4	No therapy	051	
5	No therapy	027	

TABLE 7.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases	
		7	4
1	No therapy	056	059
2	No therapy	052	060
3	Iron therapy	082	092
4	No therapy		049

TABLE 8.—RESULTS OF THERAPY ADMINISTRATION ACCORDING TO PERIODS
(Gm. hemoglobin per 100 cc. blood per day)

Donation		No. of cases			
		11	5	3	2
1	Iron therapy	068	072	076	072
2	No therapy	046	054	062	069
3	Iron therapy		057	055	063
4	No therapy			035	030
5	Iron therapy				067

In Table 8 the iron is given in alternate periods except that it was administered after the 1st donation and withheld after the 2d, and the alternate giving and withholding of iron continued on this schedule. The results are the same as previously commented upon, *i. e.*, an increased rate of hemoglobin regeneration with iron, a diminished rate without it. In the 3d period there is no response to iron although it had been effective after the first donation.

Comment. From these results it is evident that the administration of iron to blood donors hastens the regeneration of hemoglobin and shortens the recovery period. If the drug is given continuously, and repeated blood donations are given, the effect of iron becomes less marked during the 2d recovery period and has no effect on the rate of hemoglobin regeneration during subsequent recovery periods. In most individuals who give many donations while on continuous iron therapy there is a secondary and late increase in hemoglobin regeneration after 5 to 6 donations have been given, but this is usually not as great as the first response that was obtained. On the whole there is a gradually decreasing effect from iron therapy.

The reason for the increased rate of production of hemoglobin with iron therapy is not obvious for there is no evidence of depleted

iron stores in these individuals. If it were purely a matter of replacement therapy or making iron more available, there should not be a decreasing therapeutic effect as the iron reserves become better filled with its prolonged administration. It has previously been shown that iron is retained by the body from this dosage of iron and ammonium citrates and that the storage continues over a long time.² The availability of iron and the amount of iron reserves in the body do not apparently play a part in this effect. If the results were due to an elevation in the blood serum iron⁶ it should still be effective after the long periods of iron administration, since the serum iron level should increase during the 4th and 5th postdonation periods as well as in the 1st period. The increased hemoglobin response does not seem to be logically explained on the elevated serum iron level or the iron stores of the body.

When the administration of iron is discontinued after it has been given during one or more postdonation periods there is a sharp reduction in the regenerative rate although it is maintained somewhat above the rate prevailing during the control period which was without therapy. This shows some latent action of the iron which cannot be due entirely to the serum iron level. Since the iron stores are well filled these should maintain the rate of hemoglobin regeneration at a high level but since they do not maintain this level the state of the iron reserves are obviously not playing the most important rôle.

After the rate of regeneration has once been increased by iron and then allowed to return to the normal during a period without iron, subsequent administration of iron has less effect and does not again increase the regeneration rate to the high point obtained with the first iron administration.

These features suggest that iron has a stimulating effect on hemoglobin formation which is not dependent upon changes in the level of the iron in the blood serum, the reserve supply of iron, or the availability of the iron. They are in agreement with previous findings which we have reported and which we have interpreted as evidences of stimulation.

Conclusions. The administration of iron to blood donors hastens the regeneration of hemoglobin, but the effect of iron therapy is transient. Iron therapy given after subsequent blood donations does not cause as great an acceleration as with its first administration.

Iron apparently has a stimulating effect on hemoglobin formation as well as acting as replacement therapy.

There is no evidence of bone marrow exhaustion after repeated donations.

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THE CLOTTING ACTION OF FER-DE-LANCE VENOM

BY GEORGE L. KAUER, JR., M.D.

INSTRUCTOR IN MEDICINE

ROBERT M. BIRD, M.D.

ASSISTANT RESIDENT, NEW YORK HOSPITAL

AND

PAUL REZNIKOFF, M.D.

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL SCHOOL,
NEW YORK, N. Y.

(From the New York Hospital and the Department of Medicine, Cornell University
Medical College)

Introduction. The use of snake venom as a local styptic was suggested because of its well known clotting action. Eagle³ described the coagulating effect of various snake venoms and found that the venom of the fer-de-lance snake (*Bothrops atrox*) acted as an enzyme in converting prothrombin to thrombin and fibrinogen to fibrin. The fer-de-lance venom contains, in addition to the clotting factor, powerful hemorrhagins and neurotoxins which restrict its use. In 1939, a "detoxified" product became available which manifested great clotting ability but less hemolytic and neurotoxic effects. As the experiments to be reported will show, the term "detoxified" does not mean that the venom was non-toxic.

A study of the action of this "detoxified" venom was undertaken by us in order to determine its possible use parenterally in hemorrhagic conditions. Observations were made on its effect on whole blood and on fibrinogen solution *in vitro* and on its action after parenteral injection in rabbits and dogs.

Material and Methods. The stock venom was the crude dried venom of the fer-de-lance snake. The "detoxified" venom was the product obtained by evaporation of the aqueous supernate after a 1% solution of stock venom had been shaken with an equal volume of chloroform for 48 hours. Venom dilutions were made up in 0.85% solution of NaCl. The clotting time of rabbits was measured by the capillary tube method and that of dogs by a modification of the 8 mm. tube method. The *in vitro* experiments were performed on both oxalated and heparinized normal human and normal dog blood. Blood was kept fluid indefinitely by the addition of 1 cc. of N/10 sodium oxalate solution to 9 cc. of whole blood or by the addition of 300 units* of heparin (Liquæmin, Roche-Organon) to 10 cc.

* One anticoagulant unit is the anticoagulant power necessary to keep 1 cc. of recalcified, citrated beef plasma liquid for 4 hours at 37° C.

of whole blood. Dog fibrinogen, obtained through the courtesy of Dr. Wm. De W. Andrus, was prepared according to the method of Warner, Brinkhous and Smith.¹¹ A Summerson¹⁰ photo-electric colorimeter was used to measure the turbidity of the fibrinogen-venom solutions. Prothrombin determinations were made by the method of Warner, Brinkhous and Smith¹¹ and fibrinogen was measured by the method of Bancroft, Stanley-Brown and Quick.¹

Experiments and Results. *A. In Vitro Experiments. Clotting Effect of Venom on Whole Blood:* The clotting effect of *B. atrox* venom on whole blood is shown in Table 1. Serial dilutions of both stock and "detoxified" venom were made. One-tenth cc. of each dilution was added to 1 cc. each of oxalated and heparinized whole blood. The time required for the formation of an invertible, self-supporting clot is tabulated. In any given dilution, stock venom was a more rapid clotting agent than "detoxified" venom. Heparinized blood was clotted less rapidly than oxalated blood. Lysis of the clots resulted in the presence of the higher concentrations of the venom. Stock venom in 1:4000 dilution completely lysed the clot in 6 hours; whereas "detoxified" venom in 1:1000 dilution only caused partial lysis in 24 hours.

TABLE 1.—CLOTTING TIME OF OXALATED AND HEPARINIZED DOGS' BLOOD AFTER THE ADDITION OF FER-DE-LANCE VENOM

Final dilution, venom in blood	Clotting time	
	Oxal. blood	Hep. blood
<i>A. Stock Venom</i>		
1:1000	0' 05"	0' 13"
1:2000	0' 10"	0' 17"
1:4000	0' 11"	0' 15"
1:8000	0' 17"	0' 22"
1:16000	0' 21"	0' 32"
1:32000	0' 26"	1' 31"
1:64000	0' 32"	2' 17"
1:128000	0' 55"	5' 42"
1:256000	3' 32"	13' 40"
1:512000	5' 40"	1 hr. 5'
<i>B. "Detoxified" Venom</i>		
1:1000	0' 13"	0' 14"
1:2000	0' 15"	0' 29"
1:4000	0' 23"	0' 33"
1:8000	0' 25"	1' 10"
1:16000	0' 40"	1' 55"
1:32000	0' 47"	9' 50"
1:64000	3' 15"	6' 48"
1:128000	9' 25"	40' 0"
1:256000	1 hr. 45'	4 hrs.
1:512000	4 hrs.	18 hrs.

Clotting Effect of Venom on Fibrinogen. To determine the constituents of blood which might be acted upon by venom, the effect of venom on the conversion of fibrinogen to fibrin was studied. The addition of venom to a clear, dilute fibrinogen solution results in the formation of a cloudy gel-like fibrin clot, which undergoes lysis at a rate dependent on the concentration of venom. The usual Lee and White method for the determination of clotting time could not be used to measure this reaction because any agitation of this system resulted in the immediate retraction of the fibrin clot. Thus the end-point used in this technique, *i. e.*, the formation of a self-supporting clot, was seldom obtainable.

In order to obviate this difficulty a Summerson¹⁰ photo-electric color-

imeter was used to follow the turbidity of the venom fibrinogen mixture during the clotting process and the following lysis, for after insertion of the colorimeter tube no agitation of the system is necessary. The rationale for the use of this instrument for the determination of the clotting time is as follows: The transformation of fibrinogen to fibrin is accompanied by an increase in the optical density of the system. The increased density is proportional to the amount of fibrin formed. Therefore the measurement of the resistance of this solution to the passage of light becomes a relative index of the amount of fibrin present. By this means the formation and lysis of the fibrin clot can be expressed in terms of the turbidity of the solution. Figure 1 illustrates the clotting and lytic action of "detoxified" venom on fibrinogen solution expressed in turbidity of the fibrin gel. The units of turbidity are arbitrary and represent the numbers on the colorimeter dial. The maximum reading (160) indicates the complete conversion of fibrinogen to fibrin. Time is recorded after mixture of all the constituents of the final solutions. Three experiments are represented: First (dot-dash line), a solution composed of 1 cc. fibrinogen solution, 4 cc. normal saline and 0.1 cc. (30 units) heparin was incubated at 32.5° C. for 1 hour. Then 0.25 cc. of 1% "detoxified" venom was mixed with the solution. Second (dotted line) 1 cc. fibrinogen was diluted with 4 cc. normal saline and to this mixture 0.25 cc. of 1% "detoxified" venom was added. Third (solid line), a solution composed of 0.25 cc. of 1% "detoxified" venom, 4 cc. normal saline and 0.1 cc. (30 units) heparin was incubated at 32.5° C. for 1 hour. Then 1 cc. fibrinogen was mixed with the solution. In each experiment, no change in the turbidity occurred for 13 to 20 seconds after the mixture of fibrinogen and venom. Then suddenly the turbidity increased rapidly so that within 40 to 60 seconds a very turbid, self-supporting gel was formed. Within the next 2 to 3 hours the gel underwent lysis resulting in a clear solution.

TABLE 2.—EFFECT OF THROMBIN AND "THROMBIN-LIKE" AGENTS ON FIBRINOGEN

Fibrinogen solution	Fibrin* in mg. and in % of maximum yield (measured after 1 hour)					
	0.1 cc. thrombin		0.1 cc. (1-100) detox. venom		0.1 cc. (1-5000) stock venom	
	Mg.	% max. yield	Mg.	% max. yield	Mg.	% max. yield
0.50 cc. fibrinogen + 0.50 cc. saline	680	100	590	87	610	90
0.25 cc. fibrinogen + 0.75 cc. saline	350	100	270	77	310	89
0.10 cc. fibrinogen + 0.90 cc. saline	137	100	97	71	97	71
0.05 cc. fibrinogen + 0.95 cc. saline	65	100	35†	54	35†	54

* Measured in terms of reconverted fibrinogen.

† Approximate readings.

Another method was used to corroborate the fibrinolytic action of the venom. In the determination of fibrinogen, according to the method of Bancroft, Stanley-Brown and Quick, 1 hour elapses between the mixture of the components and the recovery of the fibrin. It is apparent that when venom is used as the thrombic agent the fibrin formed is exposed to the lytic action of the venom for 1 hour. Thus the relative yield of fibrin after the action of venom on a known amount of fibrinogen is compared to the yield after action by thrombin which has no fibrinolytic power. The result may be expressed as the percentage of maximum yield. Table 2 shows this comparison. One cc. fibrinogen solution was mixed with 0.1 cc. of one of the thrombic agents; the mixture was allowed to stand 1 hour before the removal of the fibrin clot. The yield of fibrin in milligrams from thrombin and from venom is also given as a percentage comparison. The lytic action is thought to be responsible for the smaller yield from the action of venom.

B. *In Vivo Experiments.* Because of the marked clotting power of venom *in vitro*, an attempt was made to speed the clotting reaction in animals by its parenteral administration. *In vivo*, experiments were performed on white rabbits and small mongrel dogs. In some experiments the animal was in the fasting state, in others the time of the last meal was not controlled.

In rabbits, no alteration in the clotting time was observed and no local hemorrhage occurred after the subcutaneous injection of as much as 0.1 cc. of 1% "detoxified" venom. A slight and inconstant fall in the rabbit's clotting time (capillary tube method) was observed within an hour after the intramuscular injection of 1 to 2 cc. of "detoxified" venom. The determination of the clotting time by the capillary tube method was too inaccurate for measurement of small differences. After determining that intravenous doses of venom in rabbits caused an increase in coagulation time associated with a decrease in fibrinogen, it was decided to use dogs as the experimental animal and to determine the clotting time by the 8 mm. tube method using venous blood.

Seven dogs died 2 to 30 minutes after a single intravenous injection of 1 cc. or 2 cc. of 1% stock or "detoxified" venom. The animals exhibited gasping, vomiting, defecation, urination, opisthotonus, respiratory paralysis and cardiac asystole. Immediately before the injection of venom the clotting times of 2 dogs were 9 minutes, and 7 minutes, 45 seconds respectively, and their blood fibrinogen levels were normal. Blood obtained as early as 50 seconds after the injection of venom was permanently fluid and contained no fibrinogen. Large hematomata at the sites of the needle puncture occurred before death. All of the animals were autopsied shortly after death. The findings were remarkable for the absence of large or small blood clots in the chambers of the heart or in the great vessels. There was marked engorgement of the vessels of the viscera both grossly and microscopically. Stained sections of heart, lung, liver, kidney, spleen and small bowel showed no evidence of deposits of fibrin on the endothelium of the blood-vessels, on the red cells or in the capillaries. Dark-field examination of postmortem blood revealed no fibrin strands.

When only 0.1 cc. of 1% "detoxified" venom diluted to 10 cc. with normal saline was injected rapidly intravenously into each of 4 dogs, the animals survived and showed only mild toxic signs. There was no positive phase (shortening) of coagulation. In 3 dogs clotting times determined 13 minutes, 23 minutes, and 30 minutes, respectively, after injection, were indefinitely prolonged and remained prolonged for 8 to 24 hours. Blood drawn from the fourth dog 38 minutes after the injection formed a friable, non-supporting clot in 40 minutes which was lysed in 4 hours. In each dog the prothrombin levels fell from 100% to 50 or 60% of normal and remained low for as long as 48 hours. No fibrinogen was demonstrable in the blood drawn as long as 4 hours after venom injection, but it returned to the normal range in 24 hours. A single additional experiment on the effect of an intramuscular injection of 0.25 cc. of 1% "detoxified" venom in a dog was performed. The clotting time, prothrombin and fibrinogen values did not change significantly over a period of 1 hour and 25 minutes.

C. *Antivenom Experiments.* As can be seen from the above experiments, the venom was found to have a marked coagulating effect *in vitro* and a marked anticoagulating action *in vivo*. Therefore it was considered possible that two factors were involved. It was thought that an antivenom could be developed which might neutralize the anticoagulating factor and thus only the coagulating effect would be manifested *in vivo*. In an attempt to develop this antivenom, each of 3 rabbits was injected subcutaneously every 3d day for 2 months with a gradually increasing dose of venom. The total amount each rabbit received varied from 5.9 to 6.6 cc. of 1% "detoxified" venom. At the end of 2 months, blood serum was obtained from the

rabbits and was pooled. *In vitro*, 0.2 cc. of varying strengths of "detoxified" venom were mixed with an equal quantity of graded serum dilutions and incubated for 1 hour at 37° C., then kept in an ice-box for 12 hours. Marked flocculation occurred in a mixture of equal quantities of a 0.05% "detoxified" venom solution and undiluted rabbit antivenom serum. The greatest flocculation occurred when a dilute venom solution was mixed with undiluted serum. In such proportions the rabbit antivenom serum was able to nullify completely the clotting action of venom. For example, an amount of venom which clotted oxalated blood in 15 seconds was rendered impotent by the addition of antivenom serum.

CLOTTING ACTION-FER-DE-LANCE VENOM

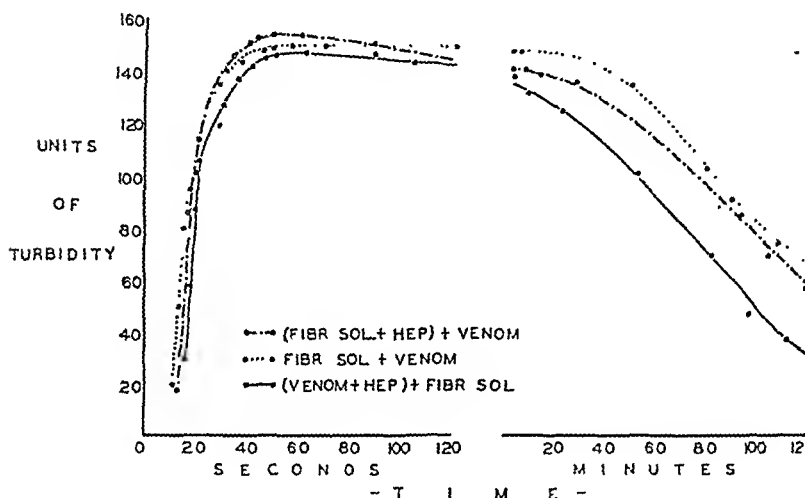


FIG. 1.

Several experiments on dogs were then performed to test the *in vivo* effect of the rabbit antivenom serum. Figure 2 illustrates the results of 4 intravenous experiments performed on 2 dogs. In Experiment A a dog was given an injection consisting of 0.15 cc. of 1% "detoxified" venom, 3 cc. rabbit antivenom serum and 2.85 cc. normal saline. This proportion of venom to antivenom serum was equivalent to that giving the greatest flocculation *in vitro*. Following the injection, the clotting time remained within the normal range while the prothrombin and fibrinogen fell to approximately 60%. In Experiment B the same dog received the same amount of venom without antivenom serum. The clotting time became indefinitely prolonged while the prothrombin and fibrinogen fell to zero. The dog died about 2 hours after the injection, having exhibited signs that accompany a lethal dose of venom. In Experiment C the proportion of venom to antivenom serum was the same as in Experiment A but the quantities were smaller. The serum was injected 40 minutes before the injection of venom. The results were comparable to those of Experiment A. Finally, Experiment D is a typical illustration of an intravenous injection of a sublethal amount of venom into a dog not protected by antivenom serum.

Two additional experiments on dogs were carried out to determine whether normal rabbit serum possessed any protective action against

"detoxified" venom. The first animal was given intravenously a solution of 0.1 cc. of 1% "detoxified" venom, 2 cc. normal rabbit serum and 1.9 cc. physiologic saline. Contrary to what might be expected, in a period of 1 hour and 30 minutes following this injection, the clotting time showed no significant change; the prothrombin fell from 100% to 64%; the fibrinogen fell to 33% of its initial value. The second dog was given intravenously a solution of 0.15 cc. "detoxified" venom, 1.9 cc. normal rabbit serum and 4 cc. physiologic saline. One hour and 2 hours following the injection the clotting times were greatly prolonged; the prothrombin was 58% and no fibrinogen could be demonstrated in the blood. Pertinent to these results are those obtained *in vitro* when 0.25 cc. of rabbit antivenom serum or 0.25 cc. of normal rabbit serum was mixed with either 1 cc. of oxalated blood or 1 cc. of fibrinogen solution. Twenty-four hours after mixture soft, friable clots were present in all tubes. The normal serum had the same degree of thrombic action as the antivenom serum.

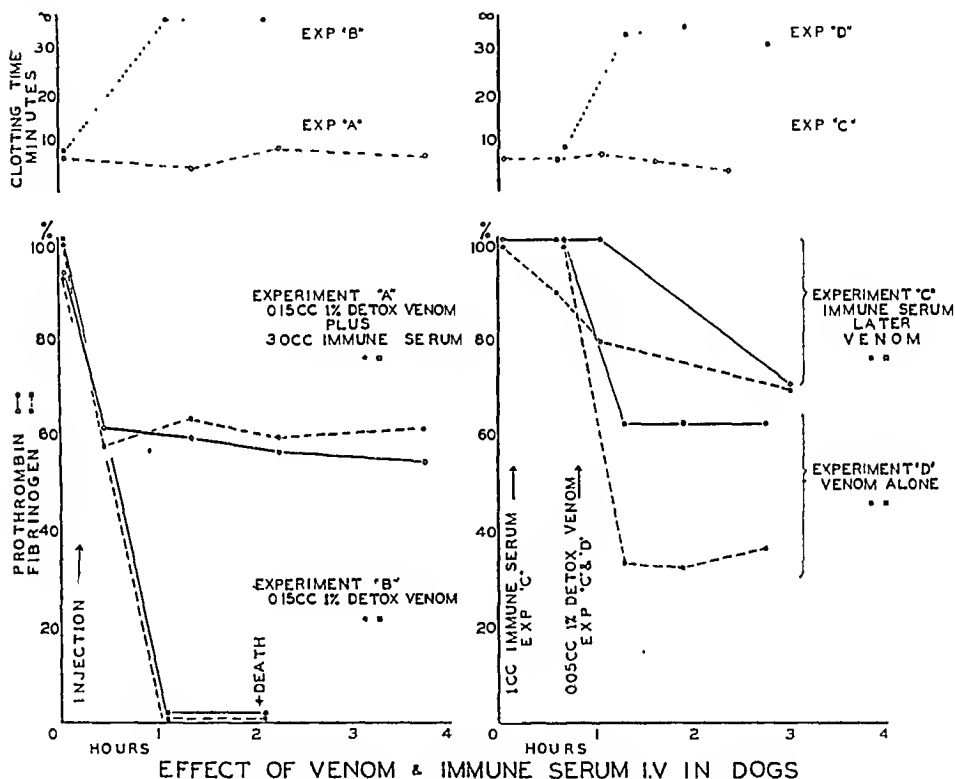


FIG. 2.

D. *Postinjection Plasma ("Plasma de Venins") Experiments.* The remaining experiments to be reported concern the clotting property of the plasma of dog's blood drawn after an intravenous injection of snake venom. One of the properties of the plasma obtained from blood which has been rendered incoagulable by venom is its ability to clot oxalated whole blood. The mechanism involved in this reaction has remained obscure although much work has been done on this problem.^{5,6} It seemed that the development of the antivenom serum described in the above experiments allowed this problem to be attacked from a new angle, since any thrombic activity of the venom could be nullified by the addition of antivenom serum. Experiments were devised to test the effect of antivenom serum on the post-injection plasma. Blood drawn both before and after the intravenous injection of "detoxified" venom was oxalated and centrifuged. The cell

free supernate was removed. This supernate will be referred to as plasma. It was repeatedly observed that the addition of postinjection plasma to normal oxalated blood resulted in the prompt clotting of the blood. No clotting occurred after the addition of pre-injection plasma or of physiologic saline. This clotting property of the postinjection plasma was always apparent if the amount of venom injected was sufficient to have caused the dog's blood to become "detoxified" venom. . . . dog was given 0.08 cc. of 1% "detoxified" venom . . . minutes later the clotting time was indefinitely prolonged, the prothrombin 30% and the fibrinogen zero. Two 18 cc. specimens of blood were drawn and oxalated, one specimen before the injection of venom, the other 30 minutes afterwards. To one-third of each of these specimens 1 cc. normal saline was added; to the second third, 1 cc. of normal rabbit serum; and to the remaining third, 1 cc. of rabbit antivenom serum. The plasmas were then removed from each of the various subspecimens and their clotting properties tested by adding 0.5 cc. of each plasma to 1 cc. normal oxalated blood and 1 cc. fibrinogen solution, respectively. Observations were made for 4 hours. No clots were observed in any of the mixtures containing pre-injection plasma or a combination of postinjection plasma and antivenom serum. Prompt clotting occurred in the mixtures containing postinjection plasma not combined with antivenom serum. The antivenom serum had thus nullified the clotting power of the postinjection plasma. Calculation of the final amount of venom in the oxalated blood and fibrinogen solution revealed that there was about 1 part in 125,000, which according to Section B of Table 1 clotted oxalated whole blood in about 9 minutes and 25 seconds. Since clotting occurred in these "plasma de venins" studies in 35 minutes it is probable that the entire thrombic activity of the postinjection plasma is due to the venom it contains as undoubtedly some of the venom is utilized in the clotting reaction.

Discussion. *In vitro*, *B. atrox* venom is an effective clotting agent in dilutions of 1:500,000. The venom acts as a thrombin as is shown by its ability to convert fibrinogen to fibrin, and also as a fibrinolysin when it is present in relative excess. Heparinized blood is clotted less rapidly than is oxalated blood. Jorpes⁸ believes that heparin is an anti-thrombin; but in the foregoing experiments, heparin did not influence the thrombic action of venom on the second phase of coagulation.

Hanut⁴ reports a positive phase of coagulation (shortening of the clotting time) after the parenteral injection of fer-de-lance venom in rabbits. Considering the errors inherent in the capillary tube method for determining clotting time, the slight reduction in the clotting time observed in rabbits following injection of large amounts of venom is not regarded as significant. Using the 8 mm. tube method for determining the clotting time, dogs show no positive phase of coagulation. Determinations were made as early as 50 seconds after the injection of venom. Intravenous injection of venom causes a fall in prothrombin and fibrinogen blood levels, but fibrinogen is the more readily affected. Both are reduced to zero when the amount of venom injected is lethal.

One of the most baffling problems raised by the experiments here reported is the striking difference between the clotting effect of fer-de-lance venom on whole blood *in vitro* and *in vivo*. The

addition of 0.002 mg. of "detoxified" venom to 1 cc. of oxalated whole blood results in solid clot formation in 1 hour and 45 minutes. When the same amount of venom per cc. of blood is injected intravenously into a dog the blood becomes indefinitely incoagulable and the animal dies in 25 minutes. Absolutely, this is of course a much larger amount of venom, which conceivably might be harmful through a selective fibrinolytic effect. There is no demonstrable prothrombin or fibrinogen in the blood drawn immediately before death. One-tenth of this amount of venom has no clotting effect on blood *in vitro*, but *in vivo* causes the blood to become incoagulable with marked depression of prothrombin and fibrinogen. There is a slow return of the animal's clotting power in 8 to 26 hours. Some workers^{7,9} have suggested that the explanation of this difference in effect might be found in the mechanical difference in precipitation of fibrin *in vitro* and *in vivo*. Regarding the fibrinogen-fibrin conversion, 3 possibilities, which would explain the incoagulable blood *in vivo*, come to mind. The circulating fibrinogen might be precipitated as intravascular fibrin plugs. Macroscopic and microscopic examination revealed no plugging of the vessels. The fibrin formed might be dispersed as finely divided particles. Dark-field examination of the incoagulable blood revealed no such particles. The fibrin formed by the venom injection might be rapidly lysed. Concerning this hypothesis, it can be shown that the amount of venom present in the circulating blood before death is of the order of 1 part in 1,000,000. Since appreciable fibrinolysis *in vitro* occurs only when the venom is present as 1 part in 1000, it is difficult to assume that the fibrin is removed from the blood by lysis. All that can be said then is that *in vitro*, fer-de-lance venom has a coagulating and an anticoagulating (fibrinolytic) action on whole blood, whereas *in vivo* (using dogs as the experimental animal) only the anticoagulating effect is evident.

The development of an antivenom serum in rabbits is described. This serum nullifies the clotting action of venom in the test tube and protects dogs from an otherwise lethal intravenous injection of venom. *In vivo*, normal rabbit serum would seem to possess a less marked protective action as shown by the fact that the clotting time may remain within the normal range while the prothrombin and fibrinogen values are depressed. *In vitro*, rabbit serum apparently possesses a weak thrombic action. This is interesting in relation to the recent work on a thrombin-like factor obtained from rabbit plasma.²

There is no evidence that dogs become sensitized to repeated parenteral administration of venom. It was observed that an animal showed progressively fewer toxic signs when injected repeatedly with a given amount of venom. Rabbits tolerate a far larger dose of venom than do dogs.

The clotting action of postinjection plasma is apparently due to the contained venom. The speed of clot formation caused by this

plasma is of the same order as that exhibited by venom in a like dilution. The clotting power of this plasma is nullified by rabbit antivenom serum.

Summary. 1. *Bothrops atrox* venom is a powerful coagulant of whole blood and fibrinogen solution *in vitro*, but when administered to dogs intravenously it produced marked prolongation of the clotting time with a reduction in prothrombin and fibrinogen.

2. An antivenom serum was developed in rabbits which completely neutralized the clotting properties of the venom *in vitro*.

3. *In vivo*, this antivenom serum modified the effect of the venom on the clotting time, blood prothrombin and fibrinogen, and also protected dogs from a lethal dose of venom.

4. Normal rabbit serum had a slight protective action against the toxic effects of intravenous administration of fer-de-lance venom.

5. The thrombic activity of postinjection plasma or "plasma de venins" was due to the venom present.

6. The difference in action of fer-de-lance venom *in vitro* and *in vivo* was not clarified by these experiments.

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A CRITICAL STUDY OF THE ACTION OF 3-3'-METHYLENEBIS (4-HYDROXYCOUMARIN) (DICOUMARIN)*

BY CHARLES S. DAVIDSON, M.D., C.M.

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL; RESIDENT PHYSICIAN,
THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL
AND

HARRIET MACDONALD, B.S.

LABORATORY ASSISTANT, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital, and the Department of Medicine, Harvard Medical School)

THE synthetic compound "dicoumarin" (3-3'-methylenebis [4-hydroxycoumarin])† isolated and synthesized by Link and his

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co-workers³ has been suggested as a substitute for heparin in clinical therapeutics by several investigators.^{1,2,15} We report here an investigation of a small group of patients treated with this substance. The investigation was undertaken to evaluate the drug critically, to compare its action with that of heparin, and to determine the precautions that should be employed when the drug is used. Our results confirm those of other investigators^{1,2,15} that the drug when administered orally prolongs the prothrombin clotting time, and to a less extent the whole blood clotting time.

Methods. Patients receiving the drug were in all instances studied daily. Coagulation time of venous blood at 37° C. was measured by a modification⁸ of the Lee and White method.⁷ Prothrombin time was determined by a modification⁹ of Quick's method.¹⁰ In all cases determination of the coagulation time was made both in glass and in lusteroid tubes. The technique for the determination of coagulation time in lusteroid is as follows: Blood was drawn with stasis from an arm vein into a syringe lined with mineral oil. The needle was removed and 2 ml. of blood were placed in each of two lusteroid tubes 100 x 13 mm. in size. The tubes were examined in the same way as the glass tubes. The normal coagulation time in lusteroid tubes using the above technique is from about 25 to 50 minutes at 37° C. It is to be emphasized that the use of a lusteroid tube not only prolongs the coagulation time above that measured in glass, but also serves to magnify small variations in it. In a like manner any errors of technique such as a poor venepuncture with admixture of tissue juice, or a tube not scrupulously clean, lead to gross changes in the coagulation time. Even though these errors were kept at a minimum, variations occurred which rendered it only a relatively crude method. Nevertheless, the use of the lusteroid technique proved to be of considerable value.

The usual procedures for intravenous bromsulphalein, hippuric acid excretion (oral), and urine urobilinogen excretion (roughly quantitative) were used in a number of patients as liver function tests, through the courtesy of Dr. Emmanuel Deutsch of the Surgical Research Laboratories of the Boston City Hospital.

Experimental. 1. *Effect on Prothrombin Concentration.* Eight individuals from 12 to 69 years old were studied. Two of them were convalescent from mild illnesses and may be regarded as normal. Of the remaining 6 subjects, 4 had thrombophlebitis, 1 had endocarditis lenta, and 1 survived suture of a puncture wound of the heart. Chart 1 shows an example of a case given dicoumarin with changes in prothrombin concentration and coagulation time measured in glass and lusteroid tubes.

The first action of dicoumarin was always displayed as a fall in the prothrombin concentration. Taking a fall to 30% of the normal prothrombin concentration as a criterion of definite effect of the drug, 3 of our patients responded within 24 hours whereas the remainder required from between 48 hours and 5 days to give such a response. One cannot predict when a response will occur in any individual following a given dose of the drug. A number of factors appear to modify the time of onset of the action: the size of the initial dose and of subsequent doses in relation to body weight; the initial level

of prothrombin concentration in the blood; an apparently large and unpredictable variation in individual response to the drug.

The effect of the substance, once low prothrombin concentrations are reached, is quite prolonged. Chart 2 shows the effect of a single large dose (15 mg./kilo) of the drug upon the prothrombin concentration of an apparently normal individual. A prothrombin concentration of below 30% of normal was maintained for 5 days and the concentration was not within normal limits for 5 more days. Most of the patients received an initial dose of from 3 to 12 mg./kilo and thereafter a daily dose of from 0.1 to 0.2 gm. Using this dosage the prothrombin concentration was maintained at very low levels and, with one exception, from 5 to 11 days were required after the drug was stopped before the concentration of prothrombin rose above 50%. When this level was reached the return to normal was always prompt.

The prothrombin time with the thromboplastin used has a normal value of from 25 to 30 seconds. The amount of prolongation of the Quick prothrombin time is of interest when interpreted as prothrombin concentration and especially when this concentration is compared with the plasma recalcification time and coagulation time of whole blood. In calculating prothrombin concentrations a curve was used which was obtained by plotting the prothrombin time of a series of appropriately modified plasmas. To accomplish this the prothrombin time was determined from varying concentrations of normal plasma, mixed with the same plasma passed through a Seitz filter 5 times. It has been shown that when plasma is passed through a Seitz filter 5 times, it becomes incoagulable with thromboplastin and calcium for more than 2 hours at least.⁶ Using this curve a prothrombin time of about 60 seconds corresponded to approximately 10%, 90 seconds to 5%, and 150 seconds to 2.5%, of the normal plasma prothrombin concentrations respectively. A prothrombin time of greater than 150 seconds was simply called less than 2.5% of normal. In many of the patients given dicoumarin the Quick prothrombin time was extraordinarily prolonged. One patient after receiving a total of 31 mg. of dicoumarin per kilogram body weight during a period of over 8 days had a prothrombin time of greater than 1 hour (Chart 1). The drug was discontinued and the next day the prothrombin time was 40 minutes and in the subsequent 6 days gradually fell from 17 minutes to 3½ minutes or about 2.5% of the normal concentration of prothrombin. These extraordinarily prolonged prothrombin times are of interest in themselves for they certainly suggest the great reserve of prothrombin in plasma above that required for coagulation. Moreover, when these figures are compared with the whole blood coagulation time on the same day one finds that when the prothrombin times were on one occasion over 1 hour and on another 40 minutes, not only did the whole blood still clot, but it did so in the relatively

short time of $17\frac{1}{2}$ and 19 minutes respectively. These whole blood coagulation times were indeed much shorter than the prothrombin time itself. The recalcification time of citrated plasma in these instances was 9 minutes and 10 minutes respectively, both normal values for the procedure and again far shorter than the prothrombin time. Thus, curiously enough, the recalcification time after the addition of an excess of thromboplastin (prothrombin time) was far longer than the recalcification time without the addition of this substance. This phenomenon was observed on several occasions and requires further study.

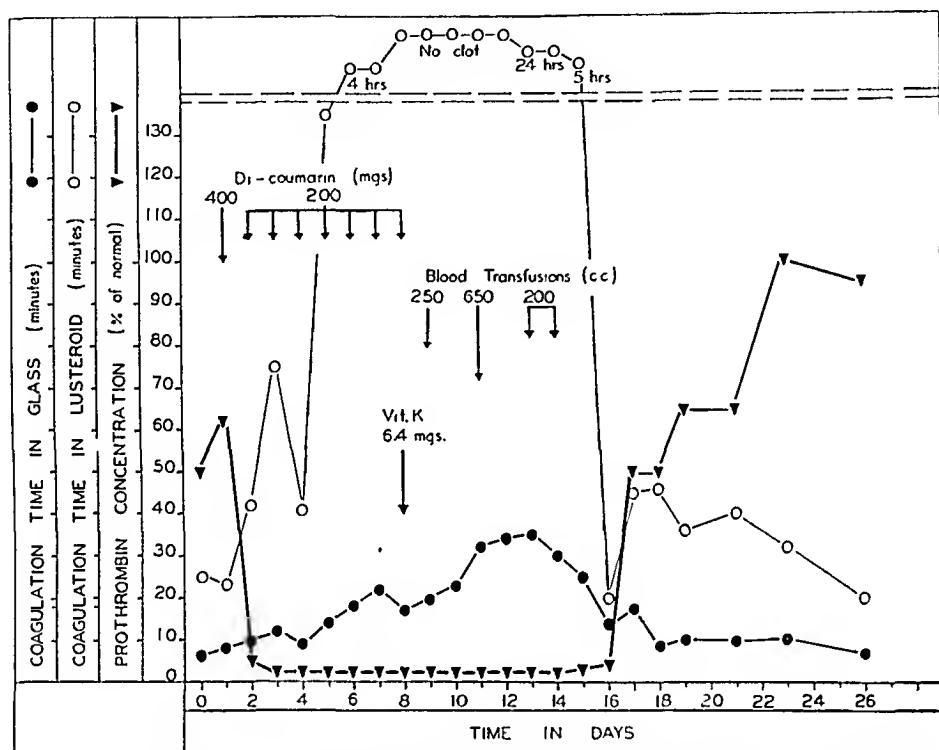


CHART 1.—Changes in the coagulation time in glass and lusteroid and the prothrombin concentration following the administration of 1.8 gm. of dicoumarin. Effect of the administration of vitamin K and whole blood transfusions.

2. *Effect on the Coagulation Time.* The effect of the administration of dicoumarin upon the coagulation time of blood measured in glass and lusteroid tubes was extremely variable. In general the coagulation time became prolonged as the prothrombin concentration reached low levels. However, there was no parallelism of the two in any one patient, and further, some of the patients had a moderately prolonged coagulation time without profound lowering of the prothrombin concentration. In general, however, the coagulation time was not significantly prolonged until the prothrombin concentration reached very low levels, usually less than 5% of normal. The coagulation time measured in lusteroid tubes showed

a much greater prolongation with reduction in prothrombin concentration, than that in glass tubes. Furthermore, the rise in clotting time in lusteroid tubes was sometimes, but not always, 24 hours earlier than the change detected in clotting time in glass. The coagulation time in lusteroid was often not measurable when the prothrombin concentration was very low due to the end-point being spread over many hours. Occasionally the blood in lusteroid tubes failed to clot under 24 hours.

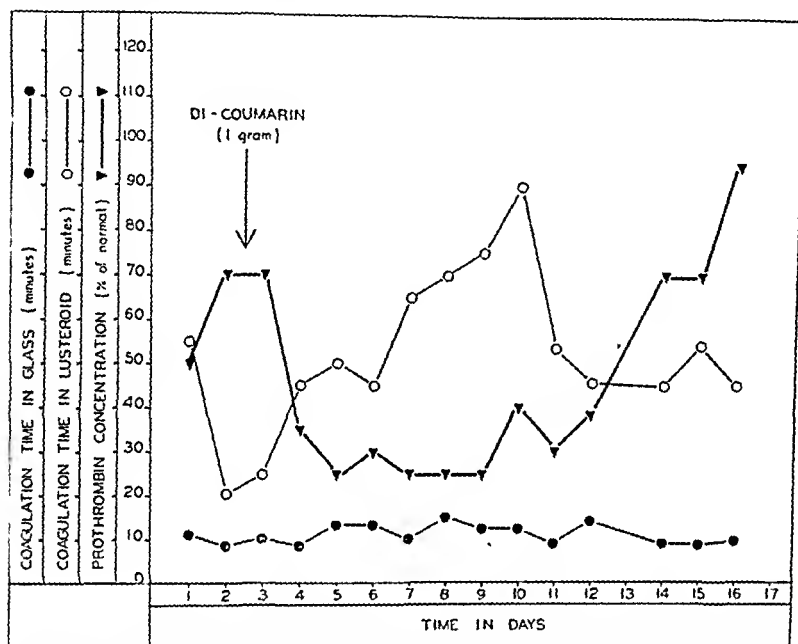


CHART 2.—Changes in the coagulation time in glass and lusteroid and the prothrombin concentration following the administration of a single oral dose of 1 gm. of dicoumarin, in a normal human.

Lozner and Taylor⁸ have shown that the effect of surfaces such as lusteroid in prolonging the coagulation time is not upon the blood platelets, but upon some property of platelet free plasma, possibly upon the "globulin substance" known to be active on but deficient in hemophilic blood. One might suppose, then, in view of the long, often very long, coagulation time in lusteroid tubes, that the plasma of patients receiving dicoumarin may have been deficient in this "globulin substance." However, we have consistently been able to hasten the coagulation of hemophilic blood, *in vitro*, as much by the addition of 0.1 ml. of plasma from patients receiving dicoumarin to 2 ml. of hemophilic blood, as by the addition of equivalent amounts of normal plasma. Thus there seems to be no modification of the action of the "globulin substance" by dicoumarin. One may suggest therefore, that whatever the rôle of the "globulin substance"

in blood coagulation may be, in plasma from patients receiving dicoumarin its lessened effectiveness probably is due to a diminished prothrombin, rather than to any change in "globulin substance" itself.

The proteolytic enzyme from plasma and serum produced by the action of chloroform, reported by Tagnon and his associates^{12,13} and said to be deficient in hemophilia,¹⁴ was found to have normal activity even when the prothrombin concentration of the plasma was only 2% to 5% of normal. From such comparative studies it would appear that dicoumarin had no effect either upon the essential activity of "globulin substance," which Howell⁵ calls "plasma thromboplastin," nor upon the proteolytic enzyme.

In most of the patients studied, the following data were obtained every 2 to 3 days: hemoglobin concentration, red cell count, hematocrit and red cell volume studies, differential and total white cell count, icteric index and platelet count. In one patient a moderate normocytic normochromic anemia developed. No such change was found in any of our other subjects. No changes in the differential or total white cell count were found, except those compatible with the changing clinical state of the patient's infection when present. Bleeding time (Duke method) was performed repeatedly on several of the patients but no prolongation was found. For example, one patient after dicoumarin administration, when the prothrombin time was greater than 1 hour and the coagulation time in glass 17½ minutes, had a bleeding time of 1 minute.

3. *Effect on Plasma Protein and Liver Function.* *Determination of plasma proteins:* albumin, globulin and fibrinogen (as fibrin) were made on several patients. There were no significant changes.

Because of its chemical constitution and because prothrombin is generally accepted as being manufactured in the liver, hepatic function tests were done on the individuals receiving dicoumarin. No significant change was found.

4. *Effect of Vitamin K and Blood Transfusion.* Our results agree with those of others^{1,2,15} that no effect on prothrombin concentration is produced when adequate doses of synthetic vitamin K were administered intramuscularly to patients receiving dicoumarin with a prothrombin concentration of less than 2.5% of normal.*

Transfusions have been reported as having a variable effect upon the coagulation time and prothrombin concentration of patients receiving dicoumarin.^{1,2,15} One of the patients under investigation received 0.9 gm. of dicoumarin and his prothrombin fell to approximately 2.5% of normal. A transfusion of 500 ml. of whole blood was administered and, as may be seen from the curve (Chart 3), a rise to 10% of the normal prothrombin concentration was obtained

* We have given 60 mg. of synthetic vitamin K parenterally to a patient receiving dicoumarin without any change in the greatly reduced prothrombin concentration.

which gradually fell again, but never to its original low level. The prothrombin concentration of the blood administered was normal. In contrast to this, another patient (Chart 1) was given repeated transfusions of whole blood without any striking effect upon the very low prothrombin concentration or prolonged coagulation time.

Discussion. It is impossible to make an adequate estimate of the clinical effectiveness of dicoumarin from a few cases and this was not the purpose of this report. However, whether associated with the drug therapy or not, clinical improvement in the cases of thrombophlebitis was uniform with the exception of 1 patient, who died of sepsis.

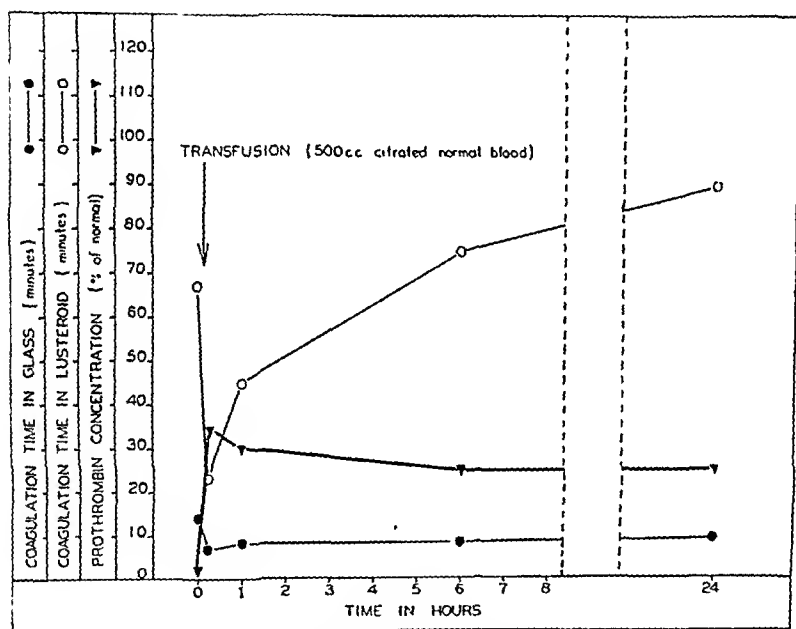


CHART 3.—Effect of a whole blood transfusion on the changes in coagulation time in glass and lusteroid and prothrombin concentration produced by the administration of dicoumarin.

No serious bleeding episodes occurred, except in the case of endocarditis lenta who had an increase in bleeding and purpuric manifestations following administration of the drug. This poor result in endocarditis lenta should be emphasized, for one is tempted to use anticoagulant therapy in this disease and other septic thromboses.

The clinical use of heparin in thrombophlebitis, phlebothrombosis, and vascular surgery has come into vogue in recent years, but its use has been hindered by the expense of the drug and by its transient effect, necessitating frequent administration or continuous intra-

venous drip. The administration of one dose of heparin will prolong the coagulation time of blood to from 30 to 60 minutes without any difficulty, and such a change may be maintained for hours or days. Following the discontinuance of heparin the coagulation time of the blood returns to normal within a few hours; the time depending upon the dose administered. For example if 5500 Connought units are given in one dose one may expect the coagulation time to be normal within 3 hours. Furthermore, if protamine (*e. g.* salamine sulphate) be administered in calculated amount, to a patient receiving heparin, the coagulation time returns to and remains normal within 5 minutes (Chart 4). Protamine has no such antagonistic effect to dicoumarin and to the present no other antidote, other than blood transfusion, is available for use in an unexpected emergency.

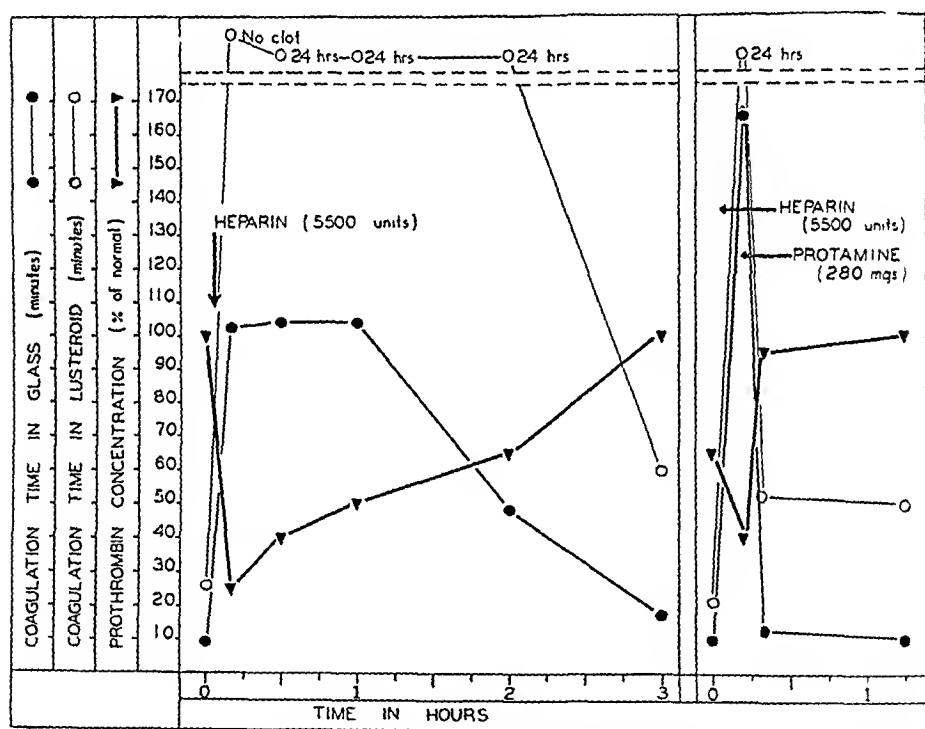


CHART 4.—Effect of administration of heparin and of heparin followed by protamine (salamine sulphate) upon the coagulation time in glass and lusteroid and prothrombin concentration in a normal human.

Dicoumarin has been proposed as a less expensive orally active substitute for heparin. It is clear that the chemical nature and mode of action of the two drugs is quite different. Heparin acts as an antieoagulant both *in vitro* and *in vivo*, whereas dicoumarin has its effect only *in vivo* and delays blood coagulation by its action upon prothrombin. Very low prothrombin concentrations must be attained before clotting is significantly delayed. Furthermore, the effect on coagulability is not constant, nor is it in any case nearly as

marked as the change after heparin administration. In the cases we have studied, enough dicoumarin compound to prolong the coagulation time significantly has an action which continues for many days after the drug is discontinued (Chart 1) and, further, this effect is not mitigated by the administration of vitamin K or transfusion of whole blood unless the drug effect is small or wearing off in which a transient effect may be noted from blood transfusion. The ineffectiveness of vitamin K on the coagulation and prothrombin time of blood of patients under dicoumarin therapy has been previously reported,^{1,2,15} as has the variable effect of blood transfusions.^{1,2,15} It has been suggested that the administration of dicoumarin compound be controlled so that the prothrombin concentration be kept within "reasonable limits."¹⁵ However, to obtain a fairly constant and significantly delayed coagulability of the blood one must reduce the prothrombin concentration to very low levels, and if this is done the effect of the drug cannot be adequately controlled. Thus one must sacrifice control for effectiveness or *vice versa* and therefore caution must be used when the administration of dicoumarin is proposed as a heparin substitute.

Summary. 1. The effect of the synthetic compound 3-3'-methylenebis (4-hydroxycoumarin)—dicoumarin—upon the coagulation of blood and upon certain blood constituents was studied in detail in a small group of patients.

2. The drug was found to act by diminishing the effective prothrombin concentration in the blood, sometimes to very small amounts.

3. The prolonged blood coagulation time observed is apparently secondary to the low prothrombin concentration, but was not constant nor was it of marked degree unless large doses of the drug are administered.

4. The coagulation time measured in "Lusteroid," although more variable than in glass, showed much greater delay in clotting than in glass after the administration of the drug. The suggestion was made that the coagulation time in "Lusteroid" indicates the true coagulation defect more closely than does glass.

5. The occurrence of prothrombin clotting times longer than recalcified plasma clotting time was observed and the possible significance of the finding discussed.

6. The relation of the abnormal clotting mechanism to other coagulation factors: foreign surface, platelets, "globulin substance," and plasma proteolytic enzyme was studied and the results discussed.

7. The effect of the administration of the drug upon blood cytology, liver function, plasma proteins, especially fibrinogen, was studied and no significant abnormalities found.

8. Vitamin K (synthetic) was found not to act in any way as an antidote to the effect of administration of the drug.

9. Whole blood transfusion was found to have only a transitory effect or no effect upon the abnormal clotting mechanism in patients receiving the drug.

10. It is suggested that the variable effect of the drug upon blood coagulability, its prolonged action after discontinuation, and its difficulty in control render the drug a poor heparin substitute, and that great caution must be used in its administration.

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SIX AUTOPSIED CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

By CONNIE M. GUION, M.D.

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, CORNELL MEDICAL COLLEGE; ATTENDING PHYSICIAN, NEW YORK HOSPITAL,

AND

ELISABETH C. ADAMS, M.D.

INSTRUCTOR IN MEDICINE, CORNELL MEDICAL COLLEGE; PHYSICIAN TO OUT-PATIENTS, NEW YORK HOSPITAL, NEW YORK, N. Y.

(From the Department of Medicine, New York Hospital)

DISSEMINATED lupus erythematosus nearly always leads to the death of the relatively young women who are its usual victims. The etiology is unknown. In the hope of adding to the understanding of the disease, 6 cases observed clinically and at autopsy at the New York Hospital are here described.

Reports of this condition already in the literature are not enumerated because of ill-defined diagnostic criteria. Some cases in the erythema group described by Osler⁵ in 1895 and 2 of the cases

described by Libman and Sacks³ in 1923 might now be listed as disseminated lupus erythematosus. Autopsied cases: Baer described 23 in 1935; Rose and Pillsbury⁷ reported 5 cases in 1939. The Reifenshteins⁶ added 1 case of their own in 1939, studied selected, reported cases, and gave an excellent review of the literature on the disease. There are many other reports^{2,4} of small numbers of cases.

Definite diagnostic criteria for this condition need to be established. The following definition has been suggested:⁶ "A diffuse peripheral vascular disease associated with lupus erythematosus and glomerulonephritis." The disease occurs in women of the child-bearing age; one probable case, however, has been autopsied in a 25-year old man and other cases have been suspected in men. Joint pains are frequent. The course is marked by exacerbations and remissions with fever, weight loss, and episodes of pericarditis and pleurisy. A terminal bronchopneumonia is the rule. The "butterfly" skin lesion is present for a long or a short time. The blood shows a secondary anemia and a leukopenia. The urine often shows small or moderate amounts of albumin with red cells and casts. Renal function may be impaired. According to present methods, blood cultures are negative. The Mantoux test may or may not be positive but evidence of active tuberculosis in connection with the disease is lacking. At autopsy involvement of the pleural and pericardial surfaces is usually found. Renal lesions are present in some cases. There may or may not be verrucous endocarditis. There is often widespread involvement of the small bloodvessels, marked by intimal proliferation and fibrosis, with degenerative changes in places in the walls, narrowing of the lumina and occasional thrombus formation.

The 6 cases here reported were observed by members of the resident and attending staff at the New York Hospital from 1936 to 1940. The histologic material has been reviewed for this report by Dr. William Dock; he has contributed the tabulations regarding the pathologic findings. The rest of the data has been taken from the hospital records.

CASE 1.—E. W., a 36-year-old, married, Swedish woman was first seen in the Out-patient Department in August 1936 complaining of a facial eruption present for 9 years. A scrofulous neck gland was removed at 10 years and pleurisy was diagnosed at 28 years. At 27 years small, red, scaly, itchy areas appeared below the eyes, spread laterally to assume a butterfly shape and disappeared after about 6 weeks. A similar eruption appeared each spring for the next 4 years, then persisted. A series of gold sodium thiosulphate and bismuth salicylate injections were given in the Out-patient Department of the New York Hospital in August and September, 1936.

In October 1936 the patient was admitted to the hospital with a temperature of 39.4° C. She was fairly well-nourished. Over the nose and entire face was a butterfly lesion, indurated and red, with elevated edges, showing marked scaling in places. The axillary nodes were enlarged. Urinalysis was normal. The hemoglobin was 94% (13.7 gm.) with 4.4 million red

blood cells. The white blood cell count was 5000 with 20% immature neutrophils. The blood Kline test was negative.

The skin lesions cleared promptly; the temperature returned to normal; treatment with bismuth and with gold sodium thiosulfate was resumed. In May 1937 the left ear began to drain. A few months later joint pains set in. Vaccine prepared from the ear discharge, and later bee venom injections, were given without improvement in the joint symptoms. The skin lesions recurred. During the following months progressive weakness and weight loss occurred with fever to 39° or 40° C. much of the time.

In August 1938 a sharp pain in the right chest with cough set in. The patient was readmitted to the hospital. She appeared cachectic. Over the entire body were numerous fiery red, scaly, dried papular lesions. There were superficial ulcerations on the buccal mucosa. There was a purulent discharge from the left ear. There were scattered râles at the lung bases. The blood pressure was 110/68. There was widespread involvement of the joints with pain and limitation of motion. After 9 days in the hospital, signs of the left lower lobe consolidation appeared; weakness and respiratory distress increased until the patient died a week later. Blood cultures were negative.

Histologically the spleen and lymph nodes showed hyperplasia, without activation, or "germinal centers"; chronic pericarditis was present; the mitral valve showed no changes nor were changes present in the kidneys save agonal degeneration of the tubules and hyperemia. There was hyaline intimal thickening of the splenic arterioles.

Anatomic Diagnosis. Chronic dermatitis with disseminated cutaneous scars; bronchopneumonia (left lower lobe); bronchitis with bronchiectasis; purulent pleurisy of the interlobar septum; bilateral serous pleural effusion; chronic pericarditis with fibrous adhesions; a focal vascular scar of one kidney; calcified tuberculous nodules in the mesenteric nodes; acute inflammation of the tracheal and tracheo-bronchial nodes; moderate hyperplasia of the superficial mediastinal, para-aortic, and iliac nodes; serous peritoneal effusion; focal fatty degeneration of the liver; petechiæ in the gastric mucosa, os uteri, and urethra; chronic arthritis with focal atrophy of cartilage of the right knee joint, with thickening of the synovial membrane and serous effusion in the joint.

CASE 2.—B. H., a 28-year-old single American woman, was admitted to the New York Hospital in December 1936 complaining of painful swollen joints for 11 months. In April 1936 a sunburn was followed by a severe skin rash diagnosed lupus erythematosus in another hospital where retinitis was observed. Anemia was also found and transfusions were given.

Physical examination showed a thin, pale woman with a large ulcer on the soft palate. The spleen was just palpable. The blood pressure was 120/70. Urine, sp. gr. 1.025, albumin, 2+ and occasion granular casts. Hemoglobin, 10.2 gm., 3.9 million red cells. The white blood cells ranged from 5000 to 10,000 per c. mm. (15 to 32% immature neutrophils and 2 to 3% eosinophils). The blood Kline test was negative; blood urea nitrogen, normal. Blood cultures were negative.

Several blood transfusions were given. Skin lesions typical of lupus erythematosus developed during the first month of observation and new mouth ulcers appeared. In January 1937 severe convulsions and signs of spasticity in the extremities occurred and cystitis developed. In March, pus appeared in the bursa over the right knee and later an abscess developed about the right hip. Hemolytic streptococci were found in these sites. A course of Prontylin was given without appreciable effect. The Mantoux test was positive to 0.01 mg. of O. T. The patient became increasingly weak and thin and died in November 1937 after several days in a delirious state with signs of terminal bronchopneumonia and pleural effusion.

Histologic examination showed much hemosiderin in the spleen; disseminated tuberculosis in the lymph nodes; no changes in the mitral valve; focal interstitial nephritis resulting from pyelonephritis and some swollen glomerular tufts. No "wire loops" or hyaline thrombi were seen in the kidneys nor was distinct periarteritis found. The splenic arteries were unchanged but there was lymphocytic infiltration about the endothelium of the trabecular veins.

Anatomic Diagnosis. Disseminated lupus erythematosus with hemorrhages in the subcutaneous tissues underlying erythematous patches; bronchopneumonia of both lower lobes with pleural effusion bilaterally; serofibrinous in type; serofibrinous pericarditis; bilateral chronic pyelonephritis with focal atrophy of the renal cortex; right urethritis, and hemorrhagic cystitis; tuberculosis of the periportal and periaortic nodes, with caseation; general lymphoid hyperplasia; a small fibrotic tubercle of the spleen; peripheral fatty degeneration of the liver; hemorrhages in the duodenal submucosa; chronic arthritis, with serofibrinous effusion in each knee joint with focal atrophy of cartilage. Ulcers were present over the sacrum, hips, and knees.

CASE 3.—G. H., a 30-year-old woman of Polish descent, was admitted to the hospital in April 1937 complaining of pain in her right chest and right upper abdomen for 3 weeks. Bilateral purulent otitis media at 22 years led to deafness. The following year joint pains in the hands began; these recurred at 24 years following an abortion and at 26 years following a normal delivery. At 29 years there occurred epistaxes, a low grade fever, petechiae, and a butterfly facial eruption for a period of several weeks.

Physical examination showed an emaciated woman who appeared chronically ill. There was a large anterior perforation of the nasal septum. Breath sounds were diminished at the lung bases and râles were present. The finger joints were stiff. Extension of the right elbow was limited. The blood pressure was 114/56. Urine: sp. gr. 1.010 to 1.021 and occasional granular casts. Hemoglobin, 10.4 gm.; 3.4 million red cells. The white blood count was 7900 per c.mm. with 4% immature neutrophils. The Kline test was 3+ on 2 occasions, but the Wassermann was negative. The red cell sedimentation rate was elevated. Blood cultures were negative.

The joint pains and stiffness gradually disappeared during a month in the hospital. Five months later the patient was readmitted with pain in the left chest and fever. Her gums were spongy and bled easily. The liver edge was 3 finger-breadths down. In December 1937 a maculopapular rash with butterfly distribution appeared on the face, gradually fading after a month. Six months later, after exposure to sunlight, the joint pains recurred and there was a transient diplopia and low grade fever. Weakness was progressive thereafter and various joints became swollen, hot, and tender and there were frequent epistaxes. The temperature rose; the spleen was palpable. In February 1939 an abscess developed about the right elbow and pericarditis with effusion appeared. These conditions cleared, the temperature returned to normal, and a weight gain occurred during the summer of 1939. In September, however, the patient was readmitted to the hospital with a rough systolic murmur over the whole precordium and signs of chronic passive congestion. The course was rapidly downhill with terminal convulsions.

Histologic examination showed intimal hyaline material in the splenic arteries with many megakaryocytes and evidence of myelopoiesis; hyperplasia of the lymph nodes without activation centers; chronic fibrous pericarditis; a chronic type of focal, chiefly subcapsular, interstitial nephritis with hyalinized thrombi. No sections were made of the heart valves. No periarteritis or focal interstitial lesions were seen in the kidney.

Anatomic Diagnosis. Atrophic dermatitis of the left pinna and superficial crusted lesions of the skin of both hands and knees; bronchopneumonia with acute arteritis of the vessels of the lungs; vegetative endocarditis (mitral, tricuspid, and aortic leaflets and mural); obliteration of the pericardial cavity; thrombi in the small arteries of the myocardium; small focal scars of the myocardium; focal interstitial and glomerulonephritis; chronic hyperplasia of the spleen; central necrosis of the liver; petechiae of the skin of the hands, legs, and trunk.

CASE 4.—E. P., a 24-year-old, single American woman, was admitted to the hospital in January 1939 complaining of a facial eruption for 5 months. The skin lesion had appeared on the nose and spread to assume a butterfly shape. Two months before admission an ultra-violet treatment had been received; 2 days thereafter the lesion became larger and the eyelids swollen; and afternoon fever developed and a weight loss occurred.

Physical examination showed a chronically ill woman with a temperature of 38° C. The eyelids were edematous. There was an angry, red symmetrical lesion over the bridge of the nose reaching to the forehead and eyebrows, scaly in places. On the hands were isolated, blotchy, red areas which faded on pressure. On the hard and soft palates were raised, red, indurated areas which seemed to arise in petechial hemorrhages. The cervical and axillary and inguinal nodes showed shotty enlargement. Urine: sp. gr. 1.004–1.014 and 1+ albumin. Hemoglobin, 11.5 gm.; with 3.6 million red cells. The white blood count was 2300 (19% immature neutrophils). The blood Kline test was negative, blood urea nitrogen normal. The red cell sedimentation rate was normal. Blood cultures were negative.

The hospital course over a period of 5 weeks was one of progressive weakness with irregular fever. There was, however, no weight loss. The skin lesions on the face regressed slightly. The lesions on the palate increased in size and became painful but never ulcerated or bled. During the sixth week in the hospital bronchopneumonia developed. The patient died 2 weeks later.

Histologic examination showed fibrous and intimal thickening in the splenic arteries; hyperplasia of the lymph nodes—no activation centers were seen; endothelial proliferation of some tufts in the kidney and in many glomeruli definite hyaline thickening producing the “wire-loop” appearance; a few eosinophilic thrombi in glomerular capillaries. No periarteritis or glomerulonephritis was seen in the kidneys. No changes were seen in the mitral or tricuspid valves. There was very early pericarditis.

Anatomic Diagnosis. General atrophic dermatitis; serofibrinous pleurisy; bronchopneumonia of both lower lobes; slight fibrinous pericarditis; moderate edema of the perirenal and perivesical tissues; slight hyperplasia of the para-aortic and mesenteric nodes; passive congestion of the spleen and liver, and a calcified nodule in the liver.

CASE 5.—M. R., a 20-year-old, single woman of Italian parentage, was first admitted to the hospital in July 1939 complaining of arthritis in various joints for over 2 years. In the summer of 1937 there was sudden onset of severe joint pains in both hands; 2 months later swelling of the hand joints began and persisted. Subsequently the patient was confined to bed on several occasions because of involvement of the other joints.

Physical examination showed a well-nourished young woman with generalized lymphadenopathy. There was spindle-shaped swelling of the interphalangeal joints of the hands and third right toe. There were signs of a small amount of fluid in the right knee joint. The blood pressure was 115/70. The urine showed a specific gravity of 1.010–1.027 and a trace of albumin. The hemoglobin was 10.6 gm. The red blood count was 3.6 million. The white blood count was 3900 with 28% immature polynuclears. The blood Kline test was \pm at one time, 3+ at another; the blood Wasser-

mann was anticomplementary. The red cell sedimentation rate was elevated. Blood cultures were negative. Biopsy of an axillary lymph node was interpreted as showing early lymphosarcoma but Hodgkin's disease was also felt to be a possibility. Roentgen ray treatments were given. The lymph nodes decreased markedly in size and the joint pains disappeared. After a week, however, a sharp pain in the lower left chest developed with night sweats and fever and edema of the face and neck appeared. The anterior cervical and submental nodes became enlarged, soft, and tender. A second series of Roentgen ray treatments was given 2 weeks after the first, but was discontinued because of evident signs of disseminated lupus erythematosus, the skin rash having occurred with butterfly distribution on the face. Biopsy of a skin lesion of the arm showed marked lymphocytic infiltration about the small vessels felt to be compatible with lupus but not diagnostic. Within a week the fever rose, the skin lesions cleared, respirations became labored and the voice hoarse. Laryngoscopy showed diffuse swelling of the vocal cords: tracheotomy was done. A terminal bronchopneumonia developed.

Anatomic Diagnosis. Atrophic dermatitis of the face, neck, and shoulders; bronchitis and bronchopneumonia; serous pleural effusion on the left; fibrinous pericarditis and ascites; edema of the lower extremities, abdominal wall, gastro-intestinal tract, retro-peritoneal tissues, and mediastinal structures of the face and neck; hyperplasia of the nodes in the cervical, axillary and abdominal regions; arthritis of the fingers, knees, and elbows; hyperplasia of the lymphoid tissue of the ileum and acute enteritis with ulceration.

Histologic examination showed fibrous thickening of the arteries of the spleen; hyperplasia of lymph nodes with numerous small activation centers; in the kidney many tufts with marked hyaline thickening—"wire-loop" lesions, and some eosinophilic thrombi; very early fibrinous pericarditis. The mitral valve was normal. No periarteritis or glomerulonephritis was seen.

CASE 6.—M. S., a 27-year-old, married American woman, was first admitted to the hospital in February 1940 complaining of attacks of stiffness in the arms and legs for 4 months. In 1936 a raised, dry, red rash covered her nose and cheeks and spread to her chin. This improved slightly under light treatment but became more severe during a pregnancy in that year. One year before admission it was noted that the hands and feet, when exposed to cold, became white and pinched distally and purplish proximally. Six months before admission intermittent stabbing pains in the shoulder blades began. Two months later the fingers, arms, and legs became stiff at intervals, sometimes with fever. The patient was observed at another hospital where pericarditis with effusion was diagnosed. Biopsy of the deltoid muscle there showed periarteritis and perivascularitis consistent with disseminated lupus erythematosus. Sulfanilamide was given with improvement for a time. After a month, stiffness of the extremities recurred and fever set in. There had been a weight loss of 27 pounds in the year.

Physical examination on admission showed a dry, scaling, irregularly confluent lesion, slightly raised and brownish, over the chin and lips. There was an irregular pink-red macular eruption over the forearms, chest, and knees. There was a diastolic gallop rhythm over the mitral area. The second pulmonic sound was markedly accentuated. The blood pressure was 110/84. The hands and feet were cold and of a pale lavender hue. The range of movements of the joints was restricted. Urine: sp. gr. 1.009–1.025, an occasional trace of albumin, and 3 to 5 red blood cells per high power field. Hemoglobin, 9.9 gm.; the red blood count 3.7 million. The white blood count was 5000 (52% immature neutrophils and 5% eosinophils). The blood Kline test was negative. The blood urea nitrogen was

normal. The red cell sedimentation rate was elevated. Blood cultures were negative.

In the hospital the macular rash faded promptly. Several attacks of abdominal pain occurred. A vesicular eruption appeared on the roof of the mouth and tongue. A deep ulceration was felt in the hollow of the sacrum. There was an irregular fever. Gradual weight loss and progressive weakness occurred. After an epileptiform convulsion, the patient died in circulatory failure during the seventh week in the hospital.

Histologic examination showed massive lymphocytic infiltration between the venous endothelium and the trabeculae in many places in the spleen. There was very early fibrinous pericarditis. The mitral valve showed no change. There was a mild myocarditis of the periarterial type. At the base of the tricuspid valve on the ventricular wall were small thrombotic masses. The kidneys showed chronic pyelitis with central abscesses and pus in the tubules. No "wire-loop" lesions were seen.

Anatomic Diagnosis. Focal atrophy of the skin of the face, right ear, chest, and shoulder; edema of the lungs with hemorrhage; fibrous adhesions between visceral and parietal layers of the pleura and peritoneum with hydropericardium and bilateral hydrothorax; acute pyelonephritis on the left; passive congestion of the spleen and liver; colitis with multiple large ulcers in the rectum and descending colon and extension of the inflammation to the parietal tissues; patent foramen ovale.

Discussion. All 6 cases were in women aged 20-36 years. Three of the patients were of American parentage; 1 was of Italian, 1 of Polish, and 1 of Swedish extraction. Four were married and had had 1 or 2 children. The occupational histories were not remarkable. One patient had had a tuberculous neck gland at the age of 10 years; 5 had had tonsillectomies.

The duration of the joint pains varied from 6 months to 6½ years. The "butterfly" skin rash was noted in all, in one 18 days before death, in another persisting for 11 years before death. All of the patients had fever at times during periods of 3 weeks to 4 years. All lost considerable weight. One patient showed postneuritic optic atrophy. Splenomegaly was found in 2 patients. The heart findings were varied. All the patients showed some tachycardia, usually paralleling the temperature rises. In the one case, however, which showed at autopsy verrucous endocarditis, no cardiac lesion was diagnosed clinically.

The urine showed from a trace to 2+ albumin in all cases, with red cells and casts in each case at one time or another. All showed slight to moderate secondary anemia. The white cell count was under 5000 in 2 cases, 5000-10,000 in 3 cases, and 12,000 in 1 case. The blood Wassermann test was negative in 4 cases, anticomplementary in one case, and 3+ at times in 1 case in whom no history or other findings suggestive of syphilis were found.

The hospital course was marked by progressive weakness in each case. The duration of the hospital stay varied from 42 days to 29 months. Bronchopneumonia was a terminal event in 5 cases, complicated in one of these by congestive heart failure. One patient developed convulsions and circulatory failure just before death.

TABLE 1.—BRIEF SUMMARY OF CERTAIN FINDINGS OF INTEREST IN 6 AUTOPSED CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS

UTION, ADAMS: DISSEMINATED

Autopsy, chief histological findings

Autopsy, chief histological findings

Autopsy, chief histological findings

TABLE 1.—BRIEF SUMMARY OF CERTAIN FINDINGS OF INTEREST															
Case	History and clinical findings					Chief gross findings	Spleen	Lymph nodes	Heart	Kidneys					
	Age	Duration of rash	Duration of joint pains	Duration of fever	Misc.										
1. EW	30	9 yrs.	2 yrs.	9 mos.	Otitis media	Chr. dermatitis; chr. pericarditis; ac. and chr. arthritis (knee); tb. of mesenteric nodes Lupus erythem. with hem. set of fibrinosis, pericarditis; ac. and chr. arthritis; tb. of spleen and ly. nodes	Subendothelial lymphocytic infiltration of trabecular veins Intimal thickening of arteries	Hyperplasia without activation centers Disseminated tbc.	Chr. pericarditis; no mitral lesion Pericarditis; no mitral lesion	Aagonal degeneration of tubules; hyperemia* Some swollen glomerular* tufts; chr. pyelonephritis					
2. BH	28	11 mos.	18 mos.	11 mos.	Cystitis; abscess of knee and hip Abscess of elbow	Atrophic dermatitis; chr. pericarditis; veg. endocarditis; myocardial scars		Hyperplasia	Chr. pericarditis (valves not sectioned)	Chronic subcapsular interstitial nephritis; a few minimal hyaline "wire-loop" lesions; rare hyaline thrombi					
3. GH	30	Few days	6 mos.	3 yrs.		Atrophic dermatitis; fibrous pericarditis	Fibrous and intimal hyaline thickening of arteries	Hyperplasia	Very early pericarditis; no mitral or tricuspid lesions	Typical "wire-loop" lesions; eosinophilic thrombi					
4. EJ†	24	6 mos.	6 mos.	3½ wks.	Calcif. tb. nodules liver	Atrophic dermatitis; fibrous pericarditis; polycystitis	Fibrous thickening of arteries	Hyperplasia with many small activation centers	Very early fibrous pericarditis; no mitral lesion	Marked "wire-loop" lesions; eosinophilic thrombi					
5. MR	20	3 days	2 yrs.	1 mo.	Lymphosarcoma diagnosed from biopsy; congenitally given	Atrophy of skin; pleural and peritoneal fibrous adhesions; ac. pyelonephritis and colitis; hydropericard. and hydrothorax	Subendothelial lymphocytic infiltration—trabecular veins	Hyperplasia	Very early fibrous pericarditis; Libman-Sacks type of endocarditis of tricuspid	Chronic pyelitis; central abscesses in tubules					
6. MS	27	1½ wks.	6 mos.	5 mos.											

ly. nodes.

* No specific lupus changes.

† Grossly calcified tb. nodules in mesenteric nodes.

Postmortem examination showed fibrin about the pleural and pericardial surfaces in all 6 cases; infiltration was, however, not seen histologically in the pericardium in 3 of these. In only one case was endocarditis detected grossly; that was verrucous in type, involving the mitral and tricuspid valves, the aortic leaflets, and the mural endocardium of the left ventricle. All 6 cases showed some evidence of kidney abnormality, chronic pyelitis with abscesses being present in one case. There was lymph node hyperplasia in all cases. The liver and spleen showed grossly chronic passive congestion. There were hemorrhages in the intestinal mucosa in 2 cases, ulceration in 2 others. There were evidences of synovial joint changes in 2 cases. Endocarditis was not confirmed histologically in the one case where it was seen grossly because sections were not made of the valves. Endocarditis, typical of the early Libman-Sacks type, was identified on the tricuspid valve on one other case, the only one in which that valve was sectioned; this lesion was not seen grossly and was unaccompanied by histologic evidence of pericarditis or specific renal lesions. Histologically the lymph nodes showed only hyperplasia, usually with no germinal centers. The spleen showed hemosiderin in 1 case, megakaryocytes and myelopoiesis in another, and perivenous infiltrate in the trabeculae of 2 cases. The kidneys showed "wire-loop" lesions in 3 cases. No periarteritis or diffuse glomerulonephritis was seen. One case showed a curious subcapsular interstitial and glomerular nephritis with only focal disseminated lesions. No case showed the curious refractile thrombi or precipitate in glomerular capillaries.

Certain significant points are listed in Table 1, page 40.

Summary. The clinical, laboratory, and autopsy findings in 6 cases of disseminated lupus erythematosus observed at the New York Hospital between 1936 and 1940 are reported.

No common etiologic basis was observed in these 6 young women. Study of the diseased tissues cast no light on the pathogenesis.

While vascular lesions were observed, none of the cases resembled periarteritis nodosa. Noteworthy was the frequent association with acute and chronic arthritis and with pericarditis.

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RHEUMATOID ARTHRITIS AND RHEUMATIC HEART DISEASE IN AUTOPSIED CASES.

By THEODORE B. BAYLES, M.D.,
RESEARCH FELLOW, ROBERT BRECK BRIGHAM HOSPITAL,
BOSTON, MASS.

(From the Medical Service of the Robert Breck Brigham Hospital and the Department of Medicine of Harvard Medical School.)

LESIONS identical with some of the rheumatic fever changes in the heart have recently been reported to be present in a little over half (56%) of patients (25) dying with apparently characteristic rheumatoid arthritis.¹ An analysis and review of the literature concerning this relationship reveals that except for the above paper, little pathologic information concerning cardiac findings in rheumatoid arthritis is available. Numerous clinical reports of the coexistence or relationship of these two diseases in the same patients or in different groups of patients have not served to clarify the situation.^{4,7,8,9,11} Pathologic studies on the subcutaneous nodules which occur in these two conditions have shown somewhat similar fundamental changes.^{6,10} In more recent studies, Collins⁵ and Bennett, Zeller and Bauer³ have drawn attention to certain structural and cytologic dissimilarities between these subcutaneous lesions. On the basis of morphologic data, it was usually possible for the latter authors to distinguish the nodules occurring in rheumatic fever patients from the nodules occurring in patients with rheumatoid arthritis. Because of these observed differences it was suggested that the lesions may be due to different agents.

Since the question of the coexistence or relationship of these two diseases is at present in doubt, it seemed worthwhile to review the autopsied cases of rheumatoid arthritis which are available at the Robert Breck Brigham Hospital. The material presented should be regarded as added information rather than as an attempt to settle the discussion. It is further hoped that eventual clarification of these two disease entities and their interrelationship, if any, will speed the search for the causative factor or factors concerned.

Materials and Methods. Twenty-three patients with definite rheumatoid arthritic changes in their joints have been studied at autopsy at the Robert Breck Brigham Hospital since 1914. The course and clinical findings were characteristic of rheumatoid arthritis with chronic joint pain and swelling producing progressive crippling over a period of years. In some instances the presence or absence of arthritic activity at the time of death could not be definitely ascertained but in each case the clinical and roentgenographic evidence made inescapable the definite diagnosis of rheumatoid arthritic crippling of some years' duration. All cases in which there was any question of another clinical cause of joint deformity have been rigidly excluded. The history of the patients and the temporal relationships of the two disorders have been reviewed and tabulated.

The pathologic information has been obtained in most instances from the protocols of the gross and histologic findings. The criterion for the

gross diagnosis of rheumatic heart disease was gross valvular change such as thickening of the leaflet edges and retraction of the leaflet edge by the shortened chordæ tendinæ. The presence of active typical Aschoff bodies was used as the histologic criterion for the diagnosis of active rheumatic fever. Dr. J. B. Hazard performed the autopsies on Cases 7, 13 and 23 (Table 1) and reviewed this material. Four of the autopsies, Cases 3, 5, 14 and 22 (Table 1), were performed by Dr. G. A. Bennett and he kindly reviewed the material from them.

Results. The pathologic findings in the joints were well advanced in most instances as the duration of rheumatoid arthritis varied from 1 to 25 years with an average duration of over 11 years. In all patients several joints were involved grossly and showed fusiform swelling or an ankylosing deformity. When complete ankylosis was present it was either fibrous or bony with disappearance of the joint space. Joints with fusiform swelling showed at autopsy thickened reddish synovial membrane and a doughy thickening of the articular capsule and periarticular tissues. Pannus formation extending centrally over the articular surfaces of the joint cartilage was seen in each instance. The cartilage was pitted and thinned under the pannus. In the patients with joint deformity of long standing (usually over 7 years), the edges of the joint surfaces showed some chondro-osseous proliferation.

Microscopic studies of sections through the synovia and the articular capsule usually showed an inflammatory process of moderate severity. The synovial lining cells are sometimes oriented in a vertical direction. The subsynovial layers are somewhat edematous and infiltrated with lymphocytes and other forms of leukocytes, including neutrophils. There are scattered small collections of lymphocytes centered around blood-vessels. In the more active cases acute inflammatory lesions involving small blood-vessels are also noted and occasionally these seem thrombosed and often a considerable amount of acidophilic hyaline fibrin or fibrin-like material is found on or within the synovial lining tissues. Sections from the articular surfaces show a layer of vascularized and chronically inflamed connective tissue (pannus) extending over the cartilage and producing dissolution and thinning of this joint element. The underlying bone is atrophic. In the patients with arthritis of long standing, microscopic studies of the joint surfaces show that they are joined together by dense fibrous tissue pannus that is moderately infiltrated diffusely and in focal areas with lymphocytes. In some patients, this connective tissue bridge is undergoing calcification and even bone formation. The patients with the Strümpell-Marie variety of rheumatoid arthritis showed fundamentally the same pathologic processes in the joints of the spine with calcification of the spinal ligaments in all our cases. The shortest duration of this disease was 7 years in our group.

Table 1 summarizes the clinical facts and the pathologic findings in the hearts of these patients.

TABLE 1.—CLINICAL DATA AND PATHOLOGIC OBSERVATIONS ON THE HEARTS OF 23 AUTOPSED CASES OF RHEUMATOID ARTHRITIS.

No.	Sex.	Clinical diagnosis.*	Age at onset of R.A. (yrs.).	Age at death (yrs.).	History of rheumatic fever.	Age at time of R.F. (yrs.).	Age at time of cardiac diagnosis (yrs.).	Age at time of cardiac symptoms (yrs.).	Weight (gm.).	Pathologic cardiac findings at autopsy.			Cause of death.
										Valves involved.	Pericardium.	Histologic.	
1	F	R.A.*-II.I.D.*	31	53	.	.	52	Never	100	Mitr. thickening and retraction	Active adherent throughout	Healing inflammatory pericarditis	Br. pneum., pul. tuberc.
2	F	R.A.-R.R.D.	(29-35)?	19	.	.	10	10	435	Mitr. sten.	Healed adherent patch	Inact. rheum. myo-card. and valv. changes	Mult. chr. emboli, sub-ac. bact. endocarditis.
3	M	R.A.-R.H.D. (Strumpell-Marie)	15 24	35	+	13	13	Never	360	Sl. mitr. sten., aortic sten.	Normal	Inact. rheum. myo-card. and valv. changes	Chr. hem., subac. bact. endocarditis.
4	M	R.A.-R.H.D. (Strumpell-Marie)	11	51	.	.	18	51	610	Aortic sten.	Normal	Inact. rheum. myo-card. and valv. changes	Cardiac failure.
5	F	R.A.	45	69	.	.	Postmortem	Never	530	Sl. mitr. sten.	Normal	Inact. rheum. valv. changes	Br. pneum.
6	M	R.A.	34	42	.	.	Postmortem	Never	Sl. enlarged	Sl. mitr. sten.	Normal	Not reported	Cerebral thrombosis.
7	F	R.A. (Still's)	11	12	.	.	(Adhesive pericarditis) 12	12	310 (3 X normal)	None	Healed adherent throughout	No rheum. changes	Cardiac failure, acute staph. endocarditis.
8	F	R.A.	17	72	260	None	Healed adherent throughout	No rheum. changes	Br. pneum.
9	M	R.A. (Strumpell-Marie)	31	42	±	5 (hoarseness)	.	.	310	Art. scler. plaques, aortic mitr. pul. mon.	Normal	No rheum. changes	Amyloidosis, nephritis.
10	F	R.A.	59	69	190	None	Normal	No rheum. changes	Purulent peritonitis.
11	F	R.A.	36	41	360	None	Normal	No rheum. changes	Rupt. esoph. varic. cirrhosis of liver.
12	F	R.A.	35	46	170	None	Normal	No rheum. changes	Postop. shock.
13	M	R.A.	23	35	310	None	Normal	No rheum. changes	Postop. staph. septice-mia.
14	F	R.A. (Strumpell-Marie)	24	41	.	.	37	Never	300	None	Normal	No rheum. changes, patent tunc. arter.	Carcinoma of lacert.
15	F	R.A.	42	59	Normal	None	Normal	No rheum. changes	Volv. br. pneum.
16	M	R.A.	25	32	+	17	.	.	290	None	Normal	Not reported	Chr. glom. nephritis.
17	M	R.A.	37	44	+	15	.	.	110	None	Normal	No rheum. changes	Erysipelas, amyloidosis.
18	F	R.A.	69	76	325	None	Normal	No rheum. changes	Carcinoma of uterus.
19	M	R.A. (Strumpell-Marie)	21	31	250	None	Normal	No rheum. changes	Staph. septicemia.
20	M	R.A. (Strumpell-Marie)	51	58	300	None	Normal	No rheum. changes	Postop. fat embolus.
21	M	R.A. (Strumpell-Marie)	25	37	330	None	Normal	No rheum. changes	Chr. nephrit. br. pneum.
22	F	R.A. (Still's)	9	27	330	None	Normal	No rheum. changes	Pul. tuberc. br. pneum.
23	M	R.A.	15	23	280	None	Normal	No rheum. changes	General amyloidosis.

Gross Lesions in the Heart. Six (Cases 1 to 6) of 23 cases of rheumatoid arthritis had cardiac changes at autopsy characteristic of those usually found subsequent to rheumatic fever with cardiac involvement. Four of these 6 cases showed varying degrees of mitral stenosis and 1 had aortic stenosis. Case 3 had slight mitral stenosis and moderate aortic stenosis of 22 years' standing. The weight of the hearts of these patients varied from 360 to 610 gm. with an average weight of 477 gm.

Cases 1 and 2 also had gross pericardial involvement. Case 1 showed an active adherent pericarditis obliterating the pericardial space while Case 2 had a healed adherent patch of pericarditis.

Two additional patients (Cases 7 and 8) had adhesive non-constricting pericarditis. One (Case 7) was healing and occurred concomitantly with very active rheumatoid arthritis (Still's disease) in a 12-year-old girl; the pericardial and pleuropericardial adhesions produced cardiac hypertrophy (340 gm.) but there were no endocardial changes before or after death and multiple sections of the pericardium and myocardium showed no Aschoff nodules or other pathognomonic changes of active rheumatic fever. In the second (Case 8) the pericarditis was found to be healed and thinly fibrous in a 72-year-old woman with no history of rheumatic fever; in this case the heart weighed 260 gm., here again rheumatic stigmata were absent.

The cardiac lesions not consistent with those of rheumatic fever found in 13 of the remaining 14 cases were mild arteriosclerotic changes in the older patients and consistent with their age. In none of these were the cardiac changes lethal. The remaining patient (Case 14) had a symptomless congenital ductus arteriosus, diagnosed antemortem.

Histologic Lesions. In no case did the histologic examination disclose active or inactive rheumatic changes in the tissue which might not have been apparent at the gross examination. In only 1 of the 6 cases with gross cardiac changes did the histologic examination reveal activity of the lesions with changes that may have been due to active rheumatic fever. Case 1 had at autopsy a healing inflammatory pericarditis in the presence of active pulmonary tuberculosis and terminal bronchopneumonia. The activity of this pericarditis might have been due to the pulmonary infection or the rheumatic fever state, but neither Aschoff nodules or tubercles were found in the sections. Therefore it was not possible to conclude more than that this lesion might represent an active rheumatic fever change, but that it may be entirely dependent upon the pulmonary infection. The fact that 3 of Cases 2, 3, 4 and 5 had terminal pulmonary infection without even questionable active rheumatic fever changes in the tissues could be interpreted to favor the possibility that the active tissue changes in Case 1 might be due to rheumatic fever. In Case 5 there was healed rheumatic

mitral valve thickening with terminal platelet deposits, but no active rheumatic lesions were seen. Histologic examination revealed inactive rheumatic fever changes in the valve leaflets and myocardium in the other cases (Cases 2, 3 and 4, Table 1).

Clinical Observations and Comment. There were 12 female and 11 male patients in this series, and of the latter, 5 had a Strümpell-Marie type of involvement. Three of each sex had rheumatic changes in the heart at autopsy. Rheumatoid arthritis of the usual type had about the same frequency of cardiac changes as did the Still or Strümpell-Marie varieties.

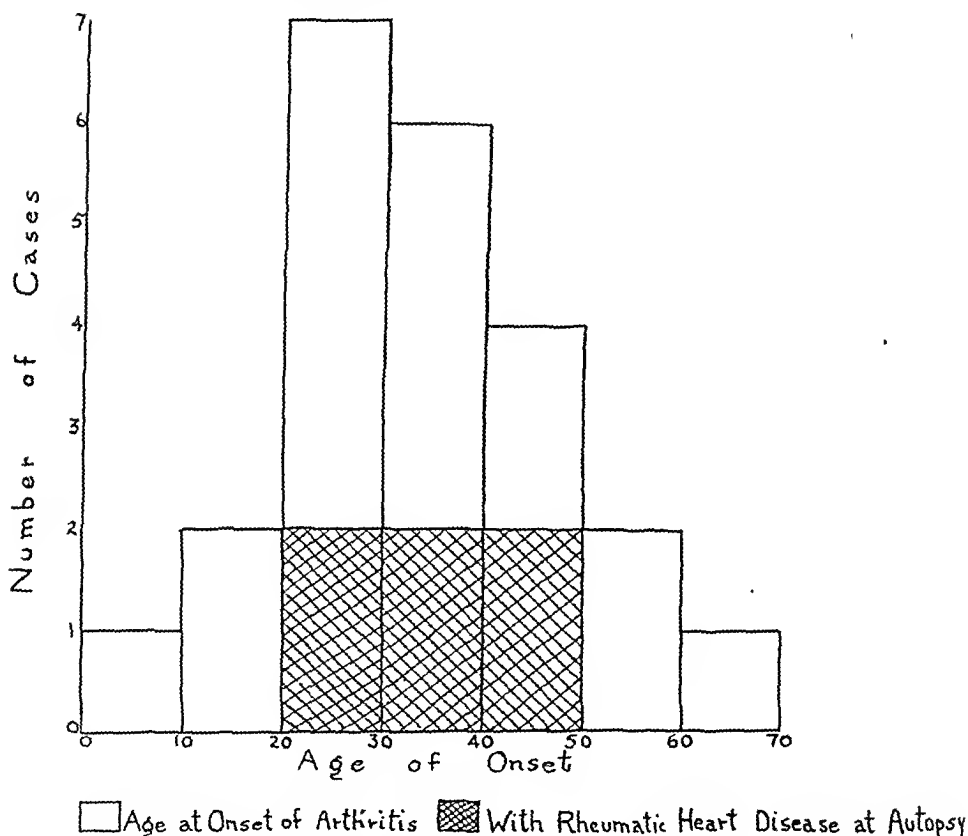


FIG. 1.—Incidence of rheumatic heart disease at autopsy as related to the age of onset of rheumatoid arthritis.

Figure 1 reveals no tendency for the age of onset to have any effect on the incidence of cardiac changes due to rheumatic fever. The average age of onset of rheumatoid arthritis of patients without cardiac changes was 29, 3 years less than the average for those with cardiac changes, 32 years.

Of the 6 cases with rheumatic cardiac changes 3 had a rapid onset of their arthritis, 1 moderately rapid and 2 insidious.

Three patients (Cases 3, 16 and 17) gave a definite clinical history of rheumatic fever but only Case 3 had subsequent rheumatic cardiac changes demonstrable at death and these were inactive. Correcting the statistics by the exclusion of this patient, 5 of 22 patients (22%) dying with rheumatoid arthritic changes in the joints had rheumatic cardiac changes at autopsy unexplained by a known previous attack of rheumatic fever. This, while an impressive finding, is less than one-half the percentage found by Baggenstoss and Rosenberg¹ in a series of 25 cases, even when their series is corrected for the same factor.

While a series of this size does not lend itself to statistical analysis, there are three important factors which appreciably temper the importance of finding 22% with rheumatic cardiac changes at autopsy. First, in one-half of the patients in which there were rheumatic changes at autopsy the heart was the center of interest ante- and postmortem. Two died of subacute bacterial endocarditis superimposed on inactive rheumatic vulvulitis and 1 of cardiac decompensation resulting from aortic stenosis and cardiac hypertrophy. Only 3 of 19 patients (15%) dying of non-cardiac causes had rheumatic cardiac changes at autopsy. Second, 4 of this group of 23 patients (17%) had clinical signs of rheumatic heart disease antemortem. This is a significantly larger proportion than the 7% found by Dawson and Tyson⁷ and the 5% found in our clinic² in 100 consecutive rheumatoid arthritic patients. Third, as clinical activity of the rheumatoid arthritis was usually present at the time of death, it seems unusual, if the two diseases are related, that only 1 case in 23 (4%) showed signs of active rheumatic fever and even in this one, these signs were not pathognomonic but only suggestive. These observations appear to make this group selected rather than usual, but why they should come to autopsy more than an unselected group is not clear, unless the type of fatal illness led to hospitalization and more intensive study. It is well known that sufferers of rheumatoid arthritis do not die of this disease and that many die of other causes in nursing homes or in their own homes where facilities for autopsy examination are not readily accessible.

Summary and Conclusions. Of 23 autopsied cases of rheumatoid arthritis, 6 were found to have changes in the heart valve leaflets and myocardium similar to those that usually follow rheumatic fever. The histologic lesions of 1 of these 6 could possibly be considered active and 5 were inactive in character. Excluding 1 patient because of definite rheumatic fever and rheumatic heart disease present in childhood, 22% had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes antemortem as compared to control groups, and the small number of cases (possibly 1) with active rheumatic fever lesions have been pointed out. The rheumatoid arthritics in this apparently selected series have a rather high incidence of cardiac

lesions similar to those that follow rheumatoid arthritis. A coincidence, a relationship of rheumatic fever and rheumatoid arthritis or the possibility that the heart disease is related to rheumatoid arthritis might be inferred from this data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, it would be safer and probably wiser, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to regard the cardiac changes as a coincidence of rheumatic heart disease and rheumatoid arthritis.

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THE RÔLE OF HEART DISEASE IN THE PSYCHOSES OF THE SENIUM.

BY SAMUEL R. ROSEN, M.D.,

RESIDENT PSYCHIATRIST, BLYTHEWOOD SANITARIUM, GREENWICH, CONN.

AND

KARL L. SMITH, M.D.,

RESIDENT PHYSICIAN, MARY MC CLELLAN HOSPITAL, CAMBRIDGE, N. Y.

(From the Neuropsychiatric Department of the Albany Hospital and Albany Medical College, Albany, N. Y.)

THE recent increased interest in geriatrics has stimulated considerable research in this field particularly in connection with the psychoses of the senium. Whereas formerly psychiatrists were content with descriptive studies of the clinical and histopathologic features of these conditions, attention now has turned toward inquiries into the physiologic changes involved.

The main focus of investigation at present centers upon cerebral metabolism. Cameron *et al.*² have suggested in psychoses of the senium that the capacity of the cerebral tissues to take up oxygen is reduced. They point out that the average arterial oxygen is definitely lower than normal (16.31 vol. %) and that arm-to-carotid circulation time is definitely lengthened (25.6 seconds). Pursuing this line of investigation further, Cameron and Rosen¹ have demonstrated that there is decreased reactivity of the intracranial vessels

in the aged as shown by a significantly diminished response to the action of histamine upon cerebrospinal fluid pressure.

The present study was undertaken from this same department to demonstrate whether circulatory insufficiency plays a significant part in contributing to the relative cerebral anoxia that obtains in these cases.

Method. The case material consisted of 43 patients suffering from psychoses associated with the senium. After psychiatric evaluation of the types of conditions involved, the cardiovascular status of each case was evaluated by careful review of medical history, physical examination, search for pertinent signs and symptoms, radiographic studies of the size of the cardiac shadow, electrocardiograms, and in doubtful instances, consultation with the Medical Service of the Albany Hospital. The classification employed was that of the New York Heart Association. The cases fell into 3 groups as follows:

1. No evidence of cardiovascular disorder (16 cases).
2. Class I heart disease, *i. e.*, organic heart disease, but capable of carrying on ordinary activities without undue fatigue, palpitation, dyspnea or chest pain (15 cases). Included in this group were 2 cases of Class IIA heart disease, *i. e.*, fully compensated but liable to develop dyspnea upon moderate exertion.

3. Class IIB and III heart disease, *i. e.*, patients with activities greatly limited manifesting signs of congestive heart failure on slight exertion (IIB) or with signs and symptoms of congestive failure while at rest (III, 12 cases). In this group the patients were obviously suffering from a toxic (cardiac) psychosis superimposed upon or aggravating the senile state.

The symptoms present in all cases were characteristic of the psychoses of the senium—loss of recent memory, confusion, disorientation, delusional and occasionally hallucinatory experiences, impaired sense of values, changes in mood and habit deterioration.

Determinations of venous pressure and arm-to-carotid circulation time were made. The venous pressures were obtained by a modification of the direct method of Taylor *et al.*¹¹ An L-shaped calibrated tube about 30 cm. in length and 3 mm. in bore is attached by an adapter to a 3-way stopcock which supports a 10-cc. syringe and a 20-gauge needle so that both syringe and needle lie in a straight line. The apparatus is autoclaved and the syringe partially filled with physiologic saline with which the manometer in turn is filled to within a few centimeters of the top. The patient* is in the recumbent position with the upper extremity supported by pillows so that an antecubital vein is 5 cm. below the angle of Luis, thus approximating the blood level in the right auricle. The horizontal arm of the manometer is adjusted to this same level (it was found that when this was done, minor changes in the position of the arm did not affect the venous pressure level because, once the needle is in the vein, a closed system exists between the manometer arm and the heart). The stopcock is then set so that venipuncture can be done. A sufficient interval is taken to allow for compression cuff venous stasis to subside. Some of the saline remaining in the syringe is then used to wash the withdrawn blood back through the needle into the vein and the manometer is switched in. The saline level in the manometer then drops to the level indicating the venous pressure and is read off on the calibrated tube in centimeters of physiologic saline. The stopcock is turned again and blood withdrawn into the syringe to test for possible clotting.

* All determinations made under basal conditions, *i. e.*, in the morning before patient has arisen from his bed or has breakfasted.

The manometer is refilled with saline and the venous pressure rechecked. The readings should not vary by more than 1 cm. The upper limit of normal is accepted as 10 cm.

Arm-to-carotid circulation time was determined by the cyanide method of Robb and Weiss¹⁰ with normal values ranging from their value of 15.6 seconds to 18.7 seconds reported by Freeman.⁴

Tests were repeated at least once on different days.

Results. (See Table 1.) The averages presented show definitely abnormal findings in the Class IIB-III group, whereas the other two groups reveal practically similar values, namely, venous pressures within the normal range, and circulation times significantly elevated but markedly lower than the average in the Class IIB-III group.

TABLE 1—VENOUS PRESSURE

Case No.	Without organic heart disease			With minimal organic heart disease			With Class IIB-III heart disease		
	Age	Ven pres	Circ time	Age	Ven pres	Circ time	Age	Ven pres	Circ time
1	60	6 0*	28 0†	64	9 3*	22 6†	68	15 5*	45 6†
2	68	5 5	26 0	69	8 0	33 6	55	8 5	24 0
3	68	8 8	24 0	67	8 8	29 8	77	8 9	28 1
4	74	6 3	27 5	79	8 8	27 0	71	5 6	26 0
5	75	7 5	24 7	76	8 5	23 2	59	15 2	27 6
6	73	6 8	24 6	60	8 6	13 5	74	12 0	15 2†
7	67		18 5	80	6 3	25 6	82	12 0	31 6
8	57	4 1	20 5	87	3 0	20 5	70	13 5	29 0
9	77	10 0†	25 0	70	9 5	26 5	65	15 5	22 4
10	85	6 8	17 5	71	8 8	19 6	74	10 5	39 7
11	65	6 5	19 0	73	7 3	17 2	73	6 8	38 0
12	63	14 5†	16 0	71	10 2†	20 5	71	11 0	25 4
13	66	6 5	16 0	70	3 6	18 6			
14	65	7 2	27 0	73	8 0	20 0			
15	60	7 2	21 0	77	16 0†	19 6			
				70	5 8	27 8			
Average	72 3	8 1	22 5	68 2	7 4	22 3	69 9	11 2	29 3

* = Venous pressure in centimeters of physiologic saline

† = Circulation time in seconds

‡ = Patient markedly agitated and tense

Discussion. Fishberg *et al.*³ and other investigators have stated that venous pressure is normal in pure left heart failure when the right ventricle is adequately functioning but is increased in right heart failure. Hitzig *et al.*⁷ and other workers have proven that in left heart failure arm-to-tongue circulation time (gluside method) is elevated while arm-to-lung circulation time (ether method)⁶ is within normal limits. The results of venous pressure and circulation time tests are therefore highly significant in determining the presence of cardiovascular disorder aside from other laboratory and clinical methods.

The abnormal values found in the Class IIB-III group confirm the status of these cases as decompensated cardiacs with right or/and left heart failure in whom the psychosis is due to a relatively marked degree of cerebral anoxia occurring during the senium. However, the similarity in the findings in the other two groups, one with minimal organic, non-symptomatic heart disease, and the other without

demonstrable organic heart disease suggests that cardiac disorder plays no significant rôle in the large group of the psychoses of the senium except as may be indicated by the moderate elevation of the circulation time. This latter may be nothing more than a mild circulatory slowing consistent with the generally decreased metabolism attending senescence, as indicated by Kise and Ochi⁸ and Lewis.⁹ Other conditions not associated with demonstrable cardiovascular disorder may have an increased circulation time as shown by Freeman⁴ in a comparative study of normal and schizophrenic subjects. However, whether or not a mild degree of subclinical arteriosclerosis may be responsible for this increase cannot be definitely ruled out. Gottlieb⁵ found a mean circulation time of 24.4 seconds for 11 patients with slight arteriosclerosis. Wortis *et al.*¹² studied a group of cerebral arteriosclerotics ranging from 59 to 97 years of age and found that the circulation time was somewhat slow concluding that there is reduced brain metabolism. One must question the comparability of their findings, however, since they regard an average of 16.6 seconds as abnormal compared to their normal of 15 seconds obtained by a method which probably did not utilize basal conditions.

Summary and Conclusions. 1. The cardiovascular status of 43 cases of psychoses in the senium was carefully evaluated.

2. Venous pressure and arm-to-carotid circulation times were determined.

3. Twelve cases had advanced cardiac disease and showed markedly abnormal values, 15 cases had minimal organic heart disease without symptomatology; and 16 had no demonstrable organic heart disease. These last 2 groups had normal venous pressures and very moderately elevated arm-to-carotid circulation times.

4. The significance of the above findings is considered and the rôle of arteriosclerosis discussed as a possible cause for the moderately elevated circulation time.

5. It is concluded that cardiac disease plays a minor rôle, if any, in the psychoses of the senium in which obvious advanced heart disease is not present.

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EXTREME TACHYCARDIA: WITH REPORT OF NON-FATAL PAROXYSMS FOLLOWING MYOCARDIAL INFARCTION.

BY JOSEPH EDEIKEN, M.D.

PHILADELPHIA, PA.

(From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, and Medical Service No. 1, Mt. Sinai Hospital.)

IN 1921 Lewis¹² and his associates showed that when the auricles of a mammalian heart were stimulated faster than 300 per minute, the auriculo-ventricular node failed to transmit each stimulus and as a result dropped beats, a 2:1 rhythm occurring with consequent slowing of the ventricles. The critical rate at which 2:1 rhythm occurs in the auricular muscle was found by Lewis to be approximately 450; the critical rate for the A-V node 270-300 per minute; the critical rate for the ventricle was intermediate. Lewis also found that if the auricles were driven at rates surpassing 300 per minute, the ventricles would beat at a lower rate. However, it was not the ventricles which failed to respond, for it responded if the stimulus was directly applied to it, but the A-V node which failed to transmit. In the mammalian heart, therefore, the upper limit of ventricular rate to be expected in extreme tachycardia arising in the auricles or A-V node should be in the neighborhood of 300 beats per minute.

A review of the literature shows that the upper limit at which the ventricles of the adult human heart can beat for a relatively prolonged period is approximately 300 per minute, although in infancy several cases with a higher rate have been recorded. Fifteen cases with a recorded ventricular rate of 300 or more per minute have been reported in the literature.^{3-8,10,14-18}

To this group we wish to add 2 cases. The first was one of acute coronary occlusion in which paroxysmal tachycardia with an extremely rapid rate occurred twice—once for a period of 12 hours with a ventricular rate of 310 per minute, and, after an interval of a day and a half, for a period of 34½ hours, with a ventricular rate of 303 per minute. Following the paroxysms, the rhythm returned to normal sinus rhythm and the patient made an uneventful recovery. The second patient was an infant, aged 22 days, who expired 2 days after the tachycardia was diagnosed.

Case Reports. CASE 1. R. G., a white woman, aged 46, was admitted to Mt. Sinai Hospital, Philadelphia, to the service of Dr. A. I. Rubenstone, on June 1, 1939. She had been in comparatively good health until May 28 when she was suddenly seized with substernal pain radiating to the left shoulder and down the left arm to the finger tips and associated with dyspnea. This attack lasted about ½ hour but similar attacks recurred at intervals of about 10 minutes. The pain was evidently not very severe inasmuch as a physician was not called. Attacks occurred during the entire day of May 29. She was relatively free of attacks on the 30th but on

May 31 the recurrence of the attacks forced her to consult a physician. The medication prescribed by him gave no relief and therefore hospitalization was advised.

She had suffered from gastro-intestinal symptoms for many years and had been aware of an elevated blood pressure but otherwise her past medical history was unimportant. Her menses had been irregular for 2 years and there had been mild menopausal symptoms.

Examination on admission revealed a very obese woman (weight 241 pounds, height 60 inches) who appeared to be in great pain. There was slight cyanosis of the lips. Percussion of the cardiac borders was difficult because of marked obesity. The heart action was regular, the sounds were distant but no murmurs were heard. The blood pressure was 96/60, but the following day was 170/110 and then dropped again to 94/60. Examination was otherwise negative except for diseased tonsils. The temperature on admission was 99° F. but rose to 101° at 8 P.M. Blood count showed 96% Hb. (13.9 gm.), 4,820,000 R.B.C. and 12,900 W.B.C. of which 68% were polymorphonuclear cells. The urine was essentially negative. The sedimentation time was 25 mm. in 60 minutes. Roentgen ray of the chest on 6-2-39 disclosed a marked enlargement of the heart and a wide supracardiac area, but the lungs were essentially negative. Electrocardiogram taken on 6-2-39 (Fig. 1, A) showed in the chest lead the typical pattern of an acute infarction involving the anterior surface of the left ventricle, but the limb leads failed to show the usual pattern of an infarction until 6-14-39 (Fig. 1, B). During this interval the patient was comfortable but the temperature was irregular and the sedimentation rate was rapid (27 mm.). On 6-22-39 the patient was awakened by severe palpitation and soon became cold and clammy. Her blood pressure was 100/80. An electrocardiogram showed extreme tachycardia of 310 per minute (Fig. 2, A). She was placed in an oxygen tent, given morphine ($\frac{1}{4}$ gr.) to allay restlessness and small doses (3 gr.) of quinidine sulphate every 4 hours. The attack lasted approximately 12 hours and the electrocardiogram taken at the end of that time showed normal sinus rhythm. Quinidine was continued and the patient was comfortable until 8 A.M. of 6-24-39, when palpitation recurred. An electrocardiogram (Fig. 2, B) showed extreme tachycardia with a rate of 303 per minute. She was again placed in an oxygen tent, opiates given for restlessness and quinidine was given in 10 gr. doses, 40 grains being given in 18 hours. In addition, powdered digitalis, $1\frac{1}{2}$ gr. t.i.d., was given. However, the attack continued and on the morning of 6-25-39, the patient appeared moribund. The blood pressure was 80/68. Nine grains of digitalis were given intramuscularly at 11 A.M. and repeated at 5 P.M. An electrocardiogram taken at 5 P.M. showed no change. At 6.30 P.M. she was examined and there was no change in rhythm. A short time later the paroxysm ceased, having lasted at least $34\frac{1}{2}$ hours. Thereafter her stay in the hospital was uneventful although her temperature continued to be slightly elevated. Her blood pressure rose and varied from 132/80 to 140/85. She was discharged from the hospital on 7-19-39. Since discharge she has been in good condition and has not experienced any attacks of cardiac pain or palpitation. Figure 1, C is the electrocardiogram taken 12-2-40.

CASE 2. T. H., a white male infant, was born of healthy parents on 5-7-42. He was examined immediately after birth and again on 5-17-42 and was thought to be normal. The child was apparently in good health until the night of 5-28-42 when his mother noticed slight pallor, which was more definite on 5-29-42. At this time the maid thought the heart rate was very rapid; the mother volunteered the statement that for the preceding 4 or 5 days the heart appeared to be fast when she held the baby over her shoulder but considered it normal. On the evening of 5-29-42, the

TABLE 1.—DATA OF 17 CASES OF EXTREME TACHYCARDIA.

Author.	Age.	Sex.	Color	Diagnosis of arrhythmia.	Paroxysms.			Signs and symptoms during attack.	Other cardiac abnormalities.	Associated conditions.	Out- come.	Effect of treatment.	Record
					Number.	Longest.	Record vent. rate, per min.						
1 McKenite, 1911	47 yrs.	M	W	Par. tachy.	Numerous	30-60 min.	290-300	Livid; very weak in Noae attacks		None	R	None during extreme tachy.; later flutter; dig. produced fibrillation, then normal rhythm	Poly-gram E.C.G.
2 Blackford and Willis, 1918	32 yrs.	F	W	Aur. flutter	Repeated	2 hrs.	300	Severe palpitation	None	Exophth. goiter	R	Dig. produced fibrillation but flutter returned on withdrawal; cured by thyroidec.	Poly-gram
3 Werley, 1925	1 days	M	W	Par. tachy.	Probably 2	At least 2 hrs.	307	Very cyanosed; liver enlarged to umbilicus; pul. edema, p.m.	Widely patent foramen ovale	No def. diag.; fever, vomit.	D	Not stated	Poly-gram
4 Russell and Ellison, 1927	3 mos.	F	W	Supravent. tachy.	Probably many	5 days	300	Complete flac; child believed dead; unconscious; later marked cyanosis and redness.	Cong. heart dis.; enlarged to right	None	R	Quinidino given; doubtful effect	Poly-gram E.C.G.
5 Langley, 1928	14 yrs.	M	W	Supranodal par. tachy.	?	?	?	None	Enlarged (?) left aur. on Roentgen clinically negative	None	R	Not stated	E.C.G.
6 Buaa, 1933	50 yrs.	M	W	Vent. tachy.	1	5 hrs.	300	Collapse; cold and clammy; marked drop in bl. pr. (60/40); pul. edema near end of paroxysm	None	Exophth. goiter	R	Quinine hydrochloride, 7 gr. ss. intraven. produced fibrillation; normal sinus rhythm 18 hrs.	E.C.G.
7 Farr and Wechsler, 1935	24 days	M	W	Extremo tachy.	6	At least 8 hrs.	300	St. cyanosis; dyspnea; liver 5 cm. below costal margin	None	None	R	Digitalis; no apparent favorable action	E.C.G.

9	Lyon, 1937	31 days	F	B	Aur. flutter	Several	10 hrs.	310-313	Dyspnea; liver enlarged and labored resp.	None	Strept. mening.	D	Not stated	E.C.G.
10	Campbell, 1937	1 mo.	M	W	Nodal par. tachy.	2	Indefinite, sev. days?	300	Dyspnea; enlarged liver	None	?	R	Dig. 2 minims t.i.d.; 1 attack stopped suddenly after 4 doses; another on 3d day	E.C.G.
11	Puglisi, 1939	10 days	F	W	Nodal par. tachy.	Probably many	?	345	Marked cyanosis and dyspnea; salivation	Roentgenogram showed enlarg. to right ? cong. heart disease	None	D	Quinidine and coramine; no effect; cardio sinus pr.; reduced rate to 285	E.C.G.
12	Berry, 1940	16 mos.	F	W	Par. tachy.	2	About 4 days	336-340	Marked pallor	None; roentgenogram showed enlarged ht. shadow during attack	G.I. upset	R	Not stated	E.C.G.
13	Hubbard, 1941	1 mo.	F	..	Aur. par. tachy.	1	38 hrs.	300	Vomiting; pallor	Cong. heart disease?	Pul. infection	R	Attack stopped spon.	E.C.G.
14	Hubbard, 1941	2 wks.	F	..	Supravent. par tachy.	2	4 days	300	Vomiting; pallor; rapid resp.; mod. enlarged liver	Roentgenogram showed mod. enlarged ht.	Xanthochromic spinal fluid	R	Digitalis, stopped attack after .1 gm. in 1 dose	E.C.G.
15	Hubbard, 1941	7 mos.	M	..	Aur. par. tachy.	1	?	305	Labored breathing	None	Pneumonia	R	Digitalis, stopped attack after .3 gm. in 1 day	E.C.G.
16	Edeiken, 1942	46 yrs.	F	W	Supravent. par. tachy.	2	3½ hrs.	310	Marked pallor; apprehension and distress; marked drop in bl. pr.	Acute infarct. of ant. surf. of left vent.; marked card. enlargement; aort. sclerosis; mod. hypertension	Menopause obesity	R	Quinidine, 1st paroxysm; digitalis, 2d paroxysm; questionable effect	E.C.G.
17	Edeiken, 1942	22 days	M	W	Supravent. par. tachy.	1	At least 2 days	320	Pallor. cyanosis; enlarged liver; resp. distress	None	?	D	Oxygen and symptomatic treatment	E.C.G.

*R = Recovered. D = Died.

child was examined by Dr. Elizabeth K. Rose and because of the extreme tachycardia was immediately admitted to the hospital of the University of Pennsylvania, service of Dr. Joseph Stokes. On examination the child appeared somewhat pale but was not cyanotic, the respirations were rapid and shallow but otherwise the infant did not appear to be in distress. The heart did not appear enlarged to percussion, the heart action was regular but extremely rapid, ≈ 320 per minute; no murmurs were heard. During examination the heart rate suddenly dropped to 160 per minute but 4 minutes later again doubled to 320 per minute. The lungs were clear but the liver was palpable 2 cm. below the right costal margin; the limbs were negative. An electrocardiogram made 5-30-42 (Fig. 2, C) disclosed a tachycardia of supraventricular origin of 320 per minute. A roentgenogram of the chest on 5-30-42 disclosed possible widening of the base of the heart; the lung fields were clear. On the evening of 5-30-42 there was slight cyanosis, the chest was clear, but the liver appeared to have enlarged. At 12.30 A.M. 5-31-42, the child suddenly awoke from sleep with a shrill cry and at this time cyanosis was more marked, respirations rapid and labored and the temperature subnormal. The child was placed in an oxygen tent but did not rally and expired on 6-1-42 at 3.15 P.M.

Postmortem examination ($1\frac{1}{2}$ hours after death) failed to reveal the cause of death; except for slight dilatation of both ventricles the heart was normal. The widened mediastinal shadow corresponded to the right lobe of the thymus. The thymus was top normal in size, 20 gm., but was not in a position to exert pressure on the heart or mediastinal structures.

Discussion. Data pertinent to the 17 cases with a recorded ventricular rate of 300 or more per minute are presented in Table 1. Certain results of the analysis of this material seem to merit discussion.

Age. The youngest patient in this series was 4 days old, the oldest 50 years. Twelve of the group were infants, others were 14, 32, 46, 47 and 50 years of age. Not only has the majority of cases occurred in infants but the fastest recorded rates and the longest paroxysms have also been found in infants. These observations would seem to bear out the statement frequently made that there is a greater responsiveness of the conduction system and greater elasticity of the musculature in hearts of very young children, thus enabling them to tolerate prolonged attacks of rapid heart action and make a rapid and apparently complete recovery.

Status of the Heart. Of the 4 instances (Cases 3, 9, 11 and 17) in which death occurred (all infants) postmortem examination was permitted in 3 (3, 9 and 17) and in each case a normal myocardium was found; in Case 3 there was a widely patent foramen ovale and in Case 9 death was due to streptococcic meningitis. The cause of death in Cases 11 and 17 was not definitely determined but a congenital heart lesion was believed to have been present in Case 11. Another (Case 4) of the infant group had congenital heart disease and congenital heart disease was suspected in Case 13, but the remaining 6 (Cases 7, 8, 10, 12, 14 and 15) disclosed no clinical evidence of heart disease. In Case 12 Roentgen ray examination during an attack showed an enlargement of heart shadow, but this cannot be considered significant inasmuch as similar findings have

been observed by Keith and Brown,⁹ and Levine and Golden¹¹ in cases of paroxysmal tachycardia with subsequent return of the heart to normal size. In 8 of the 12 cases in the infant group, therefore, the heart was considered normal.

In the boy of 14 (Case 5) a roentgenogram disclosed a questionable enlargement of the left auricle, but on clinical examination the heart was found normal. Two cases (2 and 6) in the adult group, aged 32 and 50, had exophthalmic goiter, the tachycardia following operation in 1. In both instances, however, subsequent examinations revealed normal hearts. Our case (16) had an acute myocardial infarction.

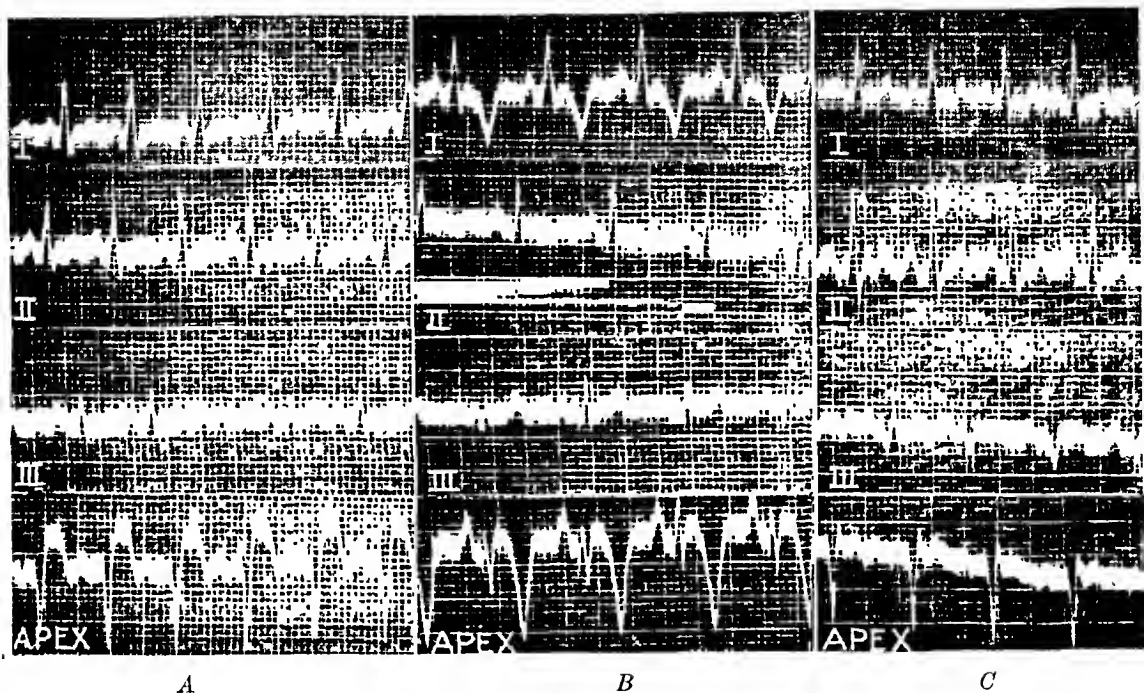


FIG. 1.—Case 1. A, Record taken 6-2-39, 2 days after attack of severe chest pain. Ventricular rate ca 150 per minute. B, Record taken 6-14-39, 2 weeks after the onset of pain and 8 days before the first paroxysm of extreme tachycardia. Rate 100. C, Record taken 12-2-40, 18 months after the attack of coronary occlusion. Rate 136.

In the majority of instances, therefore, extreme tachycardia occurred in apparently normal hearts. In only 5 of the 17 cases was there evidence of organic heart disease and in only 1 of these was there definite evidence of myocardial damage.

Associated Diseases. In 1 case (9), as stated above, streptococcic meningitis was present, 2 cases in the adult group suffered from exophthalmic goiter, in 2 cases (3 and 12) attacks seemed to be associated with a gastro-intestinal upset, and in 2 cases (13 and 15) there were pulmonary infections.

Number and Duration of Paroxysms. Both the number and duration of the paroxysms varied greatly. In 5 cases (6, 8, 13, 15 and 17) there was a single paroxysm. The number of attacks in Langley's patient is not stated, but in the remaining cases the paroxysm was repeated at least once and in some instances there were numerous attacks. The duration varied from $\frac{1}{2}$ hour in Mackenzie's case (1) to 5 days in Russell and Ellison's case (4). In the adult group the attacks were usually of short duration. Those of 12 and 34 $\frac{1}{2}$ hours observed in our cases were much longer in duration than any previously reported in an adult. The duration of the attack in Langley's patient (5) a boy of 14, was not stated. Several paroxysms in the infant group apparently lasted a number of days.

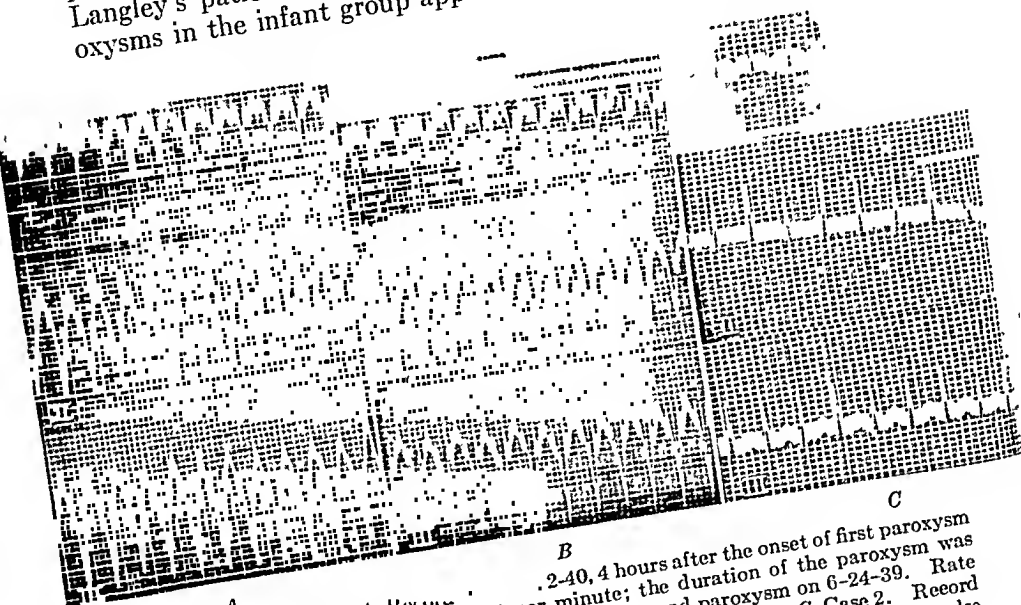


FIG. 2.—Case 1. A, Record . . . 2-40, 4 hours after the onset of first paroxysm of extreme tachycardia. Rate 310 per minute; the duration of the paroxysm was 12 hours. B, Case 1, 2 hours after the onset of second paroxysm on 6-24-39. Rate 303; the duration of the paroxysm was approximately 34 $\frac{1}{2}$ hours. C, Case 2. Record taken 5-30-42. Rate 320. Except for a period of 4 minutes during which the pulse rate dropped to 160, extreme tachycardia persisted from 5-29-42 until death of infant on 6-1-42.

Origin of the Paroxysm. The determination of the origin of the tachycardia was not ascertained with any degree of certainty except in the case (2) of 1:1 rhythm occurring during established flutter, but in only 1 case (6) was the tachycardia believed to be of ventricular origin. An examination of the electrocardiograms in our cases suggests that the paroxysms were of supraventricular origin but does not permit a distinction between auricular flutter with 1:1 rhythm and auricular tachycardia, although the halving of the ventricular rate during clinical examination of Case 17 is suggestive

of auricular flutter. Bedell² has suggested the term paroxysmal auricular tachysystole for cases of extreme tachycardia in which this distinction cannot be made, but we see no advantage in the adoption of such a term unless a need for its use to designate a hitherto unrecognized form of extremely rapid auricular beating can be demonstrated.

Symptomatology. Symptoms manifested during the attacks varied greatly in both the adult and infant group. Langley's patient (5) a boy of 14 had no symptoms, and Blackford and Willius' patient (2), a woman of 32 with exophthalmic goiter, walked several blocks to the office and during the first hour was not sufficiently inconvenienced to make any complaint. The patient reported by Berry (12), an infant of 16 months, had a tachycardia of 336-340 per minute which persisted for 4 days without marked symptoms. On the other hand, in Bunn's⁶ and in Russell and Ellison's case (4), a child of 15 months, there was complete collapse and the child was at first believed dead.

In the remaining cases, signs and symptoms usually were not marked and of these, cyanosis or pallor, dyspnea, drop in blood pressure, congestive failure, weakness and restlessness were most prominent. Loss of consciousness occurred in only 1 case (4). Pain was not an outstanding symptom in any of the cases.

Effect of Treatment. An analysis of the cases suggests that treatment was of definite value in only 6 cases; in the remainder the attacks apparently stopped spontaneously. In Mackenzie's case (1) the patient finally developed flutter and under digitalis therapy normal rhythm was restored after the flutter was converted into fibrillation. In Bunn's case (6) regarded as ventricular tachycardia, quinine hydrochloride, $7\frac{1}{2}$ gr. intravenously, produced auricular fibrillation with a ventricular rate of 150 and within 48 hours normal rhythm was restored. Cases 10, 14, and 15 were apparently favorably influenced by digitalis and Case 8 by Ouabain and quinidine. In our case, the first attack stopped after about 12 hours on quinidine therapy but the second and more prolonged one came on while the patient continued to take quinidine. Moreover, quinidine in large doses failed to stop the second paroxysm which finally ceased after large doses of digitalis. It is therefore questionable whether either quinidine or digitalis exerted any beneficial effect.

Outcome. On the basis of cases reported in the literature, Lyons stated that the prognosis in excessively rapid heart rates is good unless an associated condition is present which cannot be controlled and that excessively rapid rates occur in patients with relatively sound hearts. In Arenberg's¹ group of 39 cases of 1:1 flutter with ventricular rates of 222-300, only 1 death was attributed to the tachycardia and this was caused by a coronary occlusion due to an

antemortem clot from the left auricle. However, so far as we can determine, in no previously reported case has there been recorded an extreme tachycardia during the early stages of coronary occlusion. Although our patient recovered, it is obvious that this does not warrant a favorable prognosis in similar cases. The cause of death in 3 of the infant groups (Cases 3, 11, 17) was not ascertained and in these the possibility that extreme tachycardia may have been a major factor cannot be dismissed.

Summary and Conclusions. 1. Two cases of extreme tachycardia are added to the 15 cases previously reported with a recorded ventricular rate of 300 or more per minute; in 1 instance the tachycardia occurred during the acute stage of myocardial infarction.

2. So far as we can determine, our Case 1 is the only case in which such extreme tachycardia was recorded in the presence of acute myocardial infarction; in the other cases of extreme tachycardia the myocardium was regarded as sound.

3. Two paroxysms of extreme tachycardia occurred in the patient suffering from myocardial infarction—one lasting 12 hours with a ventricular rate of 310 per minute and another lasting $34\frac{1}{2}$ hours with a ventricular rate of 303 per minute. The onset and offset in both attacks were sudden.

4. The ventricular rate of 310 per minute is the fastest sustained tachycardia recorded in the adult human heart; more rapid rates have been recorded in infants.

5. In 9 of the 15 previously reported cases, treatment did not appear to influence the paroxysms or prevent their recurrence. It is questionable whether treatment (quinidine and digitalis) exerted any beneficial effect in stopping the paroxysms complicating acute myocardial infarction.

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THE FAMILY HISTORY IN ARTERIAL HYPERTENSION

A STUDY OF 4376 INSURANCE EXAMINATIONS

By ROBERT H. FELDT, M.D.

AND

D. E. W. WENSTRAND, M.D.

MILWAUKEE, WIS.

(From the Medical Department, Northwestern Mutual Life Insurance Company)

THE concept of a hereditary factor in essential hypertension has not been accepted by all investigators. Striking reports^{2,10} have frequently appeared of single families with a high incidence of hypertensive vascular disease. Nevertheless, statistical studies have not demonstrated convincingly that heredity is a major factor in the development of hypertension. In some papers, the criteria used to classify the family history have not been clearly defined. The care with which the family history is recorded and the age of the subjects are important variables which must be considered. Unfortunately, these factors have not always been taken into account. This paper covers the results of a controlled study of 4376 life insurance examinations in which only a slight relationship between the family history and the blood pressure was observed.

More than 25 years ago, Janeway⁴ said that his "figures suggest a subordinate and accessory influence of inheritance for the majority of patients who have hypertension." In 1923 Weitz⁹ reported a higher incidence of heart disease, edema, and apoplexy among parents of hypertensive patients than there was among parents of persons who did not have hypertension. O'Hare, Walker, and Vickers⁶ compared family histories of 300 hypertensive patients whose average age was 52, with records of 436 non-hypertensive patients whose average age was 36. A family history of apoplexy, heart disease, nephritis, arteriosclerosis, or diabetes was elicited in 68% of the hypertensive group and 37.6% of the controls. Nuzum and Elliot⁵ observed a positive family history in 30.8% of 500 patients with high blood pressure and 29.6% of 250 persons with normal blood pressure. The average age of their two groups was the same. Palmer⁷ reported on the incidence of familial vascular disease in 100 unselected patients with hypertension and 100 controls. The difference was so slight as to have no statistical significance. Ayman¹ observed that high blood pressure was more common in the offspring of hypertensive parents than it was in children whose parents had normal blood pressure. Hines³ noted a positive family history of hypertensive cardiovascular disease in 87% of 267 patients with essential hypertension and in 30% of 608 persons with normal blood pressure. The comparative ages were not stated. In a relatively small series, Thacker⁸ elicited a family history of

hypertensive cardiovascular disease in 54% of 96 hypertensive university students and in 3% of 128 students who had normal blood pressure.

Material. The 4376 persons studied consisted of all the applicants (2188) who were refused insurance by the Northwestern Mutual Life Insurance Company in 1940 and 1941 because of high blood pressure and a control series of 2188 applicants who were issued insurance in 1940 and 1941 and whose blood pressure was normal. The control group was selected at random except that age and sex were matched with the age and sex of the applicants who had high blood pressure. The subjects were all members of the white race, and, in general, they were in moderate or good economic circumstances. It cannot be said that 4376 different families were covered because certain unavoidable duplication occurred. For example, a brother and sister might have applied for insurance and, hence, the family history would be the same. Random sampling of 1062 applications showed that each of two family histories were counted twice because two pairs of brothers were involved. Therefore, the amount of duplication was negligible. In each group there were 229 (10.5%) females and 1959 (89.5%) males. The ratio of females to males was about the same as the ratio among all applicants of similar age. The average age was about 43 years, and the age distribution was as follows:

Distribution of cases.	
Ages 10-19	55
20-29	342
30-39	389
40-49	730
50-59	553
60-65	119
	<hr/>
	2188

Of the applicants who had high blood pressure, 83% showed an initial reading of 150 mm., systolic and/or 90 mm., diastolic, or more. Of the control group, 75% had an initial blood pressure under 140 mm., systolic, and 85 mm., diastolic. The examinations were made by many different examiners, most of whom would be classified as general practitioners. Every State was represented, except South Carolina, Florida, Alabama, Mississippi, Louisiana, and Texas. The examination blank is so devised that the family history is secured before the examination is made. Space is provided for recording the state of health, if living, or the cause of death, if dead, of each relative. In addition, there are specific questions regarding diabetes, apoplexy, heart disease, and kidney disease. Since the examiner does not usually take the blood pressure until the history has been recorded, disproportionately intensive questioning of hypertensive applicants is avoided.

Results. *Family History of Cardiovascular-renal Disease.* In classifying the family histories, only the parents and siblings of

the applicant were considered. The definite statement that one or more relatives, past the age of 40, had died or was ill due to heart disease, arteriosclerosis, apoplexy, Bright's disease, or high blood pressure, was accepted as evidence of familial cardiovascular-renal disease. The same criteria of classification were applied to the subjects with normal blood pressure and to those with high blood pressure. Table 1 shows that there was only a slight difference in the incidence of familial cardiovascular-renal disease. Six hundred and fifty (29.7%) of the subjects with normal blood pressure and 717 (32.7%) of those with high blood pressure had such a family history.

Family History of Hypertensive Cardiovascular Disease. In an attempt to determine the familial incidence of *hypertensive* cardiovascular disease, another classification of the family history was made. The only illnesses that were regarded as due to hypertensive cardiovascular disease were those in which the relative suffered from high blood pressure or some illness which seemed likely to be the result of hypertension. Death or illness caused by cardiac or cerebral accidents occurring between the ages of 40 and 70 was regarded as probably due to hypertension. Table 1 shows that 274 (12.5%) of the applicants with normal blood pressure had one or more instances of hypertensive cardiovascular disease among parents and siblings. Three hundred and thirty (15.1%) of the hypertensive subjects had similar histories. Again, the difference in the incidence of positive family histories is slight.

TABLE 1.—RELATION OF FAMILY HISTORY TO BLOOD PRESSURE

History of parents and siblings	2188 subjects with normal blood pressure		2188 subjects with high blood pressure	
	No.	%	No.	%
One or more cases of cardiovascular-renal disease	650	29.71 \pm .98	717	32.77 \pm 1.01
One or more cases of <i>hypertensive</i> cardiovascular disease	274	12.52 \pm .71	330	15.08 \pm 0.77
One or more cases of diabetes	66	3.01 \pm .36	82	3.75 \pm 0.40

The standard error (or standard deviation) of a percentage is calculated according to the formula: $SE = \sqrt{pq/n}$, where p is the per cent of the sample with the characteristic studied and q is the per cent without the characteristic. The n is the number of observations. The standard error of a difference between two percentages is equal to $\sqrt{(SE_1)^2 + (SE_2)^2}$.

The standard error of the difference between 29.71 \pm .98% and 32.77 \pm 1.01% is 1.41%. The actual difference (3.06%) is 2.17 times the standard error of the difference. Such a difference in one direction could occur 15 times in 1000 as a matter of chance and, therefore, the difference is probably statistically significant.

The standard error of the difference between 12.52 \pm .71% and 15.08 \pm .77% is 1.05%. The actual difference (2.56%) is 2.44 times the standard error of the difference. Such a difference in one direction could occur 7 times in 1000 as a matter of chance and, therefore, the difference is statistically significant.

The standard error of the difference between 3.01 \pm .36% and 3.75 \pm .40% is .54%. The actual difference (.74%) is 1.37 times the standard error of the difference. Such a difference in one direction could occur 85 times in 1000 as a matter of chance and, therefore, the difference is not statistically significant.

To make a stronger comparison, family histories of persons with low normal blood pressure were compared with those of persons

having high diastolic blood pressure. In the control group, there were 350 individuals past the age of 40, whose initial blood pressure was 120 mm., systolic, and 80 mm., diastolic, or less. There were 657 persons past the age of 40 in the hypertensive series whose initial diastolic blood pressure was 100 mm. (4th point), or more. As will be seen in Table 2, the incidence of familial hypertensive cardiovascular disease between the ages of 40 and 65 was 12.9% in persons with low normal blood pressure, as compared with 16.9% among those with high diastolic blood pressure. Even when persons with these extremes of blood pressure were studied, the difference in the incidence of familial hypertensive cardiovascular disease was not great.

TABLE 2.—COMPARISON OF FAMILY HISTORY IN APPLICANTS WITH LOW NORMAL BLOOD PRESSURE AND THOSE WITH HIGH DIASTOLIC PRESSURE

	No. of subjects Ages 40 to 65	One or more cases of hypertensive cardiovascular disease among parents and siblings	
		No.	%
Initial blood pressure 120 and 80 or less . . .	350	45	12.86 \pm 1.79
Initial diastolic blood pressure 100 or more . . .	657	111	16.89 \pm 1.45

The standard error of the difference between $12.86 \pm 1.79\%$ and $16.89 \pm 1.45\%$ is 2.30%. The actual difference (4.03%) is 1.75 times the standard error of the difference. Such a difference in one direction could occur 40 times in 1000 as a matter of chance, and, therefore, the difference may be statistically significant.

Family History of Diabetes. Some investigators have included familial diabetes with the cardiovascular diseases, but in this study diabetes was counted separately. Table 1 shows that 3% of the control subjects and 3.7% of the hypertensive applicants had a family history of diabetes. Since the difference is not statistically significant, it appears likely that a family tendency toward diabetes is not related to the subsequent development of hypertension.

Comment. By clinical concepts, the subjects were inadequately studied. It is impossible to classify the hypertension observed, but it is widely held that 80 to 90% of arterial hypertension is due to so-called essential hypertension. The determination of blood pressure is a simple procedure which can be accurately performed by most insurance examiners. Any inaccuracies would be offset by the large number of subjects involved. The well-known fact that persistent elevation of the blood pressure, as found on insurance examinations, has been associated with high death rates, and that normal blood pressure leads to normal death rates, validates blood pressure readings obtained on insurance examinations. More extensive clinical study would be desirable, but it is not necessary for comparative purposes.

It is important to know that the family history was not elicited more searchingly in the hypertensive group than it was in the control subjects. In the present series, it is reasonable to assume that the family history was recorded with about the same degree of care in each group. It is illogical to make a statistical comparison

without taking into account the obvious fact that the incidence of positive family histories is higher among the old than among the young. This is clearly shown by examining the records of the 2188 persons with normal blood pressure, as shown in Table 3. In this *control* group, the incidence of a positive family history of cardiovascular-renal disease was 10.8% in the 2d and 3d decades of life, 28.7% in the 4th and 5th decades, and 42.6% in the 6th and 7th decades. In the hypertensive subjects, similar age variations were observed.

TABLE 3.—INFLUENCE OF AGE ON FAMILY HISTORY IN 2188 APPLICANTS WITH NORMAL BLOOD PRESSURE

Ages	Subjects	One or more cases of cardiovascular-renal disease among parents and siblings	
		No.	%
10-29	397	43	10.83 ± 1.56
30-49	1119	321	28.69 ± 1.35
50-65	672	286	42.56 ± 1.91

A critical examination of the published material raises doubts as to the significance of heredity in the development of hypertension. Certainly, the figures reported here do not support the contention that it is of major importance. In this paper, the strongest possible comparison was made, *i. e.*, between the family histories of persons with low normal blood pressure and of subjects with high diastolic blood pressure. Surely, if hypertension is primarily a familial disease, a major variation in the incidence of hypertensive family histories should be observed, and yet only a slight difference was noted. Perhaps factors other than inheritance will be proved to be the cause of most cases of essential hypertension.

Summary. A brief review of the literature and analysis of family histories taken from life insurance examinations are reported. In this series of 4376 applicants, the incidence of familial cardiovascular disease was only slightly greater among hypertensive persons than it was among persons with normal blood pressure. There was no significant difference in the familial incidence of diabetes. It appears unlikely that heredity is of primary importance in the etiology of hypertension.

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THE EFFECT OF ANTIPRESSOR KIDNEY EXTRACT, ANGIOTONIN, METHYL GUANIDINE AND TYRAMINE ON CARDIAC OUTPUT AS MEASURED BY THE BALLISTOCARDIOGRAPH IN HYPERTENSIVE AND NORMAL PERSONS

By R. D. TAYLOR, M.D.

AND

IRVINE H. PAGE, M.D.

INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research and the Indianapolis City Hospital)

THE action of angiotonin on both isolated and intact hearts reproduces some of the physiologic phenomena which have come to be associated with the cardiodynamics of arterial hypertension in man. Methyl guanidine and tyramine also exhibited some properties not unlike those of angiotonin, while having other properties distinctly different. It seemed of interest to compare the effects of these three pressor agents both on cardiac output and the contour of the ballistocardiographic curve to ascertain which of the three more nearly fulfilled the requirements of the naturally occurring pressor agent in hypertensive patients.

The significance of these results would be strengthened if it could be shown that not only does angiotonin reproduce the ballistocardiographic curve common in hypertensives, but that lowering the hypertensive's blood pressure by means of angiotonin-destroying kidney extracts causes reversion to the curve characteristic of normotensives. It is, then, the province of this communication to explore further the possibility that angiotonin is the chemical mediator of experimental renal and human hypertension.

Methods. In addition to 15 hypertensions, to be considered later, 6 healthy young laboratory workers were given the pressor drugs angiotonin and methyl guanidine in intravenous infusions of normal saline to maintain a constant elevation of arterial blood pressure. Tyramine was given subcutaneously to the same persons. The antipressor renal extracts were prepared by Dr. O. M. Helmer and given as daily intramuscular injections to patients with malignant or essential hypertension. These patients had been studied for 6 months or more in the Lilly Clinic. Estimations of cardiac output were made with the ballistocardiograph using the area method of Starr, Rawson, Schroeder and Joseph.^{6*} All tracings were taken after a 15-minute rest period and at least 2 hours after a meal. When absolute values are given, the correction of 18.5% is made as suggested by Cournand, Ranges and Riley³ to make the ballistocardiograph values correspond with those obtained by the direct Fick method.

Results. 1. *Tyramine Injection.* Stroke volume increased from 49, 48 and 58 cc. to 63, 52 and 69 cc., in 3 normal persons when

* Recently Starr and Schroeder detected a mathematical error in their paper J. Clin. Invest., 19, 438, 1940. This error was excluded in the calculation of these data.

hypertension was induced by injection of tyramine. Calculated on the basis of the reduced pulse rate (*i. e.*, 108, 68, 80 reduced to 68, 60 and 54 beats per minute), cardiac output was decreased in the 3 experiments.

TABLE 1.—EFFECT OF TYRAMINE, METHYL GUANIDINE SULFATE AND ANGIOTONIN ON ARTERIAL BLOOD PRESSURE, STROKE VOLUME, PULSE RATE AND CARDIAC OUTPUT* OF NORMAL YOUNG ADULTS

Case	Before				After			
	Blood pressure, mm. Hg	Stroke volume, cc.	Pulse rate	Cardiac output	Blood pressure, mm. Hg	Stroke volume, cc.	Pulse rate	Cardiac output
1. <i>Tyramine</i>								
1 . .	134/82	49	108	3.05	236/130	63	68	2.47
2 . .	118/82	48	68	1.88	192/110	52	60	1.80
3 . .	116/60	58	80	2.68	152/93	69	54	2.15
2. <i>Methyl Guanidine Sulfate</i>								
1 . .	100/60	64	72	2.66	132/94	57	58	1.91
2 . .	124/72	53	76	2.33	158/94	46	56	1.48
3 . .	96/70	40	82	1.90	160/110	34	54	1.06
3. <i>Angiotonin</i>								
1 . .	96/70	40	82	1.90	152/110	36	54	1.12
2 . .	124/72	53	76	2.33	154/100	47	64	1.73
3 . .	120/80	46	84	2.23	180/120	31	90	1.61
4 . .	100/68	57	70	2.30	140/110	46	54	1.43
5 . .	132/72	58	82	2.74	140/110	45	70	1.82
6 . .	102/78	57	78	2.57	146/110	45	62	1.61

* In liters per minute per square meter of body surface.

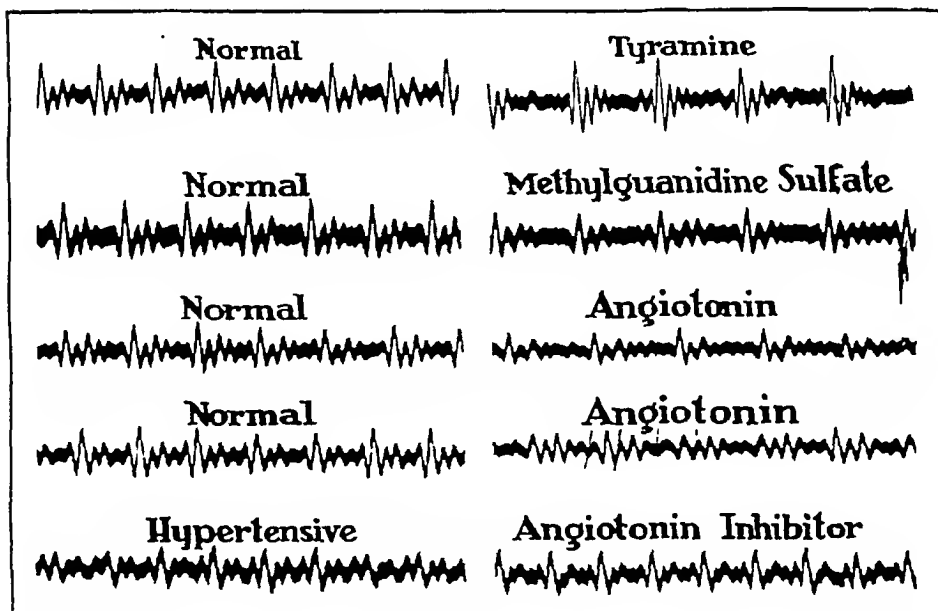


FIG. 1.—Ballistocardiograph tracing of normal persons after injection of tyramine (100 mg.), methyl guanidine sulfate (3 gm.) and angiotonin. The last pair of tracings are of a hypertensive patient before and after treatment with kidney extract.

The ballistocardiograph tracing of 1 of these subjects before and after injection of tyramine is illustrated in Figure 1. The blood

pressure before administration was 116/60 mm. Hg and after tyramine was 152/92 mm. Hg. The tracing clearly demonstrates the bradycardia as well as the increased stroke volume.

Of importance was the fact that highly unpleasant symptoms accompanied the hypertension. These began with consciousness of the slow, forceful beating of the heart, soon to be followed by almost unbearable headache and throbbing in the neck. The latter, along with nausea and vomiting, persisted though diminished in intensity, up to 6 hours.

2. *Methyl Guanidine Sulfate*. Methyl guanidine sulfate in amounts sufficient to produce similar elevation in arterial pressure decreased stroke volume instead of increasing it as did tyramine. But bradycardia also occurred, resulting in sharp fall in cardiac output (Table 1). These changes are seen in the second tracing in Figure 1. The arterial blood pressure rose in this subject after administration of methyl guanidine from 100/60 to 132/94 mm. Hg. The symptoms produced were not as severe as those with tyramine, but nevertheless very disagreeable. Tingling and numbness of the lips and mouth were followed by generalized numbness, precordial oppression, cold perspiration, faintness and nausea.

3. *Angiotonin*. Injection of angiotonin in 6 normal persons caused only slight bradycardia in 5 of the subjects. In the sixth the rate increased 6 beats per minute. But all of them exhibited decreased stroke volume (Table 1) and cardiac output. The third and fourth tracings in Figure 1 illustrate these changes in the ballistocardiographic record. It is of special interest that hypertension produced by angiotonin was not associated with marked symptoms. The bradycardia passed unnoticed.

4. *Contour of Tracings*. Comparison of the tracings in Figure 1 with Figure 3 show a difference in the form of the waves in some hypertensives as compared with normal subjects.

The waves following hypertension induced by tyramine differ strikingly from those observed in patients with essential hypertension. Those resulting from methyl guanidine differ less. Angiotonin, on the other hand, elicits ballistocardiographic waves closely resembling those seen in some hypertensive patients. As Starr has pointed out, however, the contour of the waves in hypertension is not characteristic of hypertension alone.

5. *Action of Kidney Extracts*. Twelve patients with malignant hypertension and 3 with essential hypertension were treated with antipressor angiotonin-destroying kidney extract in sufficient quantity to reduce arterial pressure (Table 2). The mean arterial pressure (diastolic + one-half the pulse pressure) of these patients before treatment was 174 mm. Hg with a maximum of 214 and minimum of 154 mm. Hg. The average cardiac output was 2.0 liters per minute per square meter of body surface. After treatment the average mean arterial pressure was 140 mm. Hg.

No increase in average pulse rate occurred. But the average cardiac output was increased from 2.0 to 2.5 liters per minute per square meter of body surface (Fig. 2).

TABLE 2.—EFFECTS ON ARTERIAL BLOOD PRESSURE, PULSE RATE, STROKE VOLUME AND CARDIAC OUTPUT OF ANTIPRESSOR RENAL EXTRACTS OF 15 HYPERTENSIVES

Case	Before				After				Diagnosis*
	Blood pressure, mm. Hg	Pulse rate	Stroke volume	Cardiac output	Blood pressure, mm. Hg	Pulse rate	Stroke volume	Cardiac output	
1	230/120	80	37	1.71	198/100	84	43	2.08	M
2	218/130	70	44	1.78	164/90	64	49	1.81	M
3	220/128	68	45	1.76	174/102	66	51	2.16	M
4	228/146	94	37	2.01	180/116	104	42	2.41	M
5	206/145	96	42	2.33	138/96	96	57	3.16	M
6	254/134	100	34	1.96	220/115	96	37	2.16	M
7	207/136	74	50	2.14	176/118	84	58	2.81	M
8	188/145	92	32	1.70	176/122	92	40	2.12	M
9	220/120	82	37	1.75	178/100	76	61	2.67	M
10	190/140	68	43	1.69	191/118	78	51	2.29	M
11	194/112	70	44	1.78	134/84	66	69	2.63	E
12	204/112	72	46	1.91	152/82	66	78	2.97	E
13	212/120	90	55	2.86	186/108	94	60	3.26	M
14	242/180	94	33	1.79	170/116	86	44	2.18	M
15	200/118	76	43	2.19	180/108	76	55	2.41	E

* E = Essential, M = Malignant.

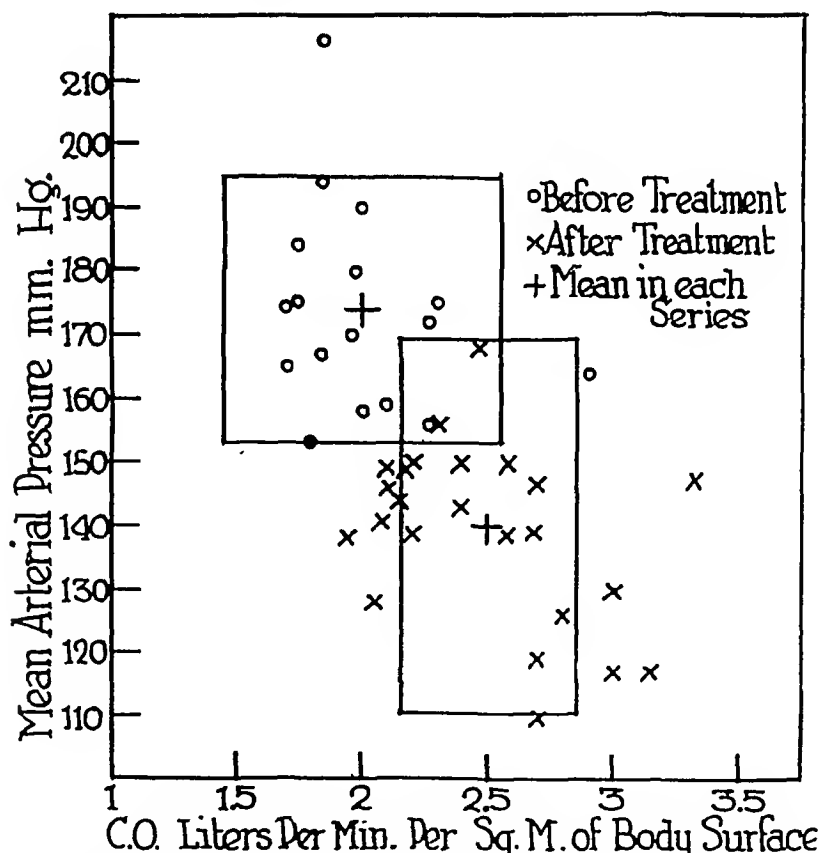


FIG. 2.—Relationship of cardiac output to mean arterial pressure (i. e., diastolic pressure + one-half pulse pressure) before and after lowering the arterial pressure of hypertensive patients with kidney extract.

Inspection of the ballistocardiographic tracings before and after treatment clearly shows increase in stroke volume and absence of tachycardia (Fig. 4). When the "early M" complexes of Starr

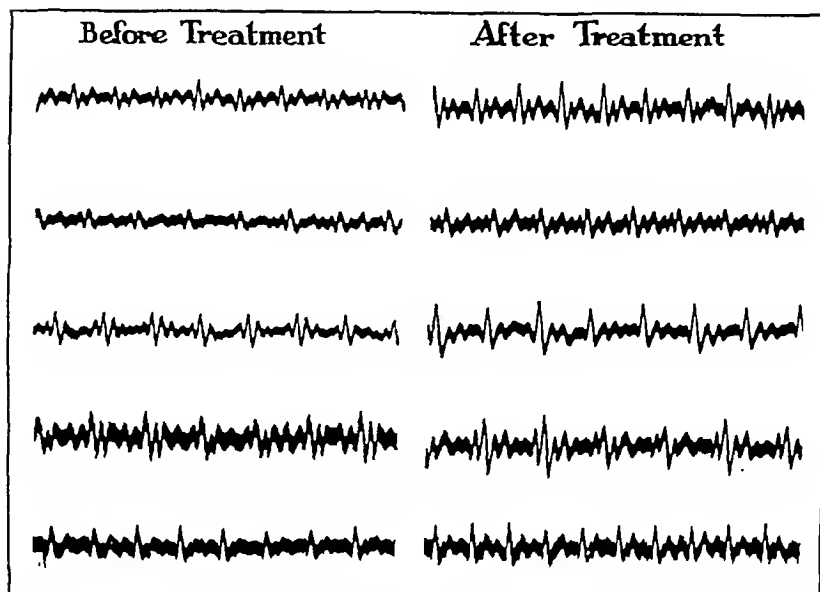


FIG. 3.—Ballistocardiographic tracing of 5 hypertensive patients before and after their arterial pressure was lowered by kidney extract.

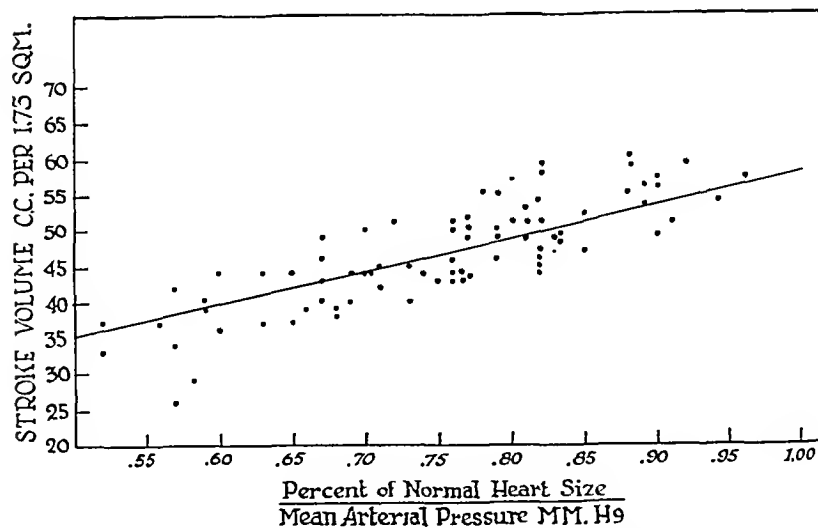


FIG. 4.—Relationship of stroke volume to $\frac{\text{cardiac enlargement}}{\text{mean arterial pressure}} \left(\frac{\text{C.E.}}{\text{Pm}} \right)$ in 81 hypertensive patients.

were present before treatment they usually disappeared or were modified toward the form of the normotensive. This is especially clear in the first tracing in Figure 3. The average blood pressure of this patient before treatment was 206/145 mm. Hg, stroke volume 42 cc., and pulse rate 96 beats per minute. After treatment the blood pressure was 138/96 mm. Hg, stroke volume 57 and pulse rate 90. We believe the ballistocardiographic tracing taken after treatment to be normal in contour.

6. *Estimation of Stroke Volume.* The stroke volume as measured by the ballistocardiograph of a group of 25 healthy young adults is given in Table 3. These results are for comparison with those in Table 4 in which similar measurements on 81 hypertensive patients are recorded. In the latter table the results are arranged in relation to the mean arterial pressure. An attempt has been made, as will be discussed later in this communication, to estimate the stroke volume from a formula based on cardiac enlargement and mean pressure. It should be emphasized that these calculations are

TABLE 3.—STROKE VOLUME PER 1.73 SQ. M. OBSERVED IN 25 HEALTHY NORMOTENSIVE YOUNG ADULTS

Case	Mean arterial blood pressure, mm. Hg	Sex	Stroke volume per 1.73 sq. m. in cc.
1	80	F	55
2	80	F	55
3	80	M	57
4	84	F	53
5	84	M	57
6	88	M	59
7	89	F	53
8	90	M	57
9	93	M	62
10	94	F	58
11	95	F	52
12	95	F	55
13	95	M	65
14	98	F	55
15	99	F	53
16	100	F	52
17	100	F	51
18	100	M	66
19	104	F	52
20	104	M	60
21	108	M	56
22	109	F	49
23	109	M	58
24	109	M	57
25	112	M	63
		12 M 13 F	
Average	96	59 8 53 3	56 1

recorded rather as a stimulus for further exploration of the problem rather than a solution. Application of the ballistocardiograph to clinical problems is admittedly in its infancy and interpretation of the curves may subsequently be greatly altered. Despite this, records of observation with this method seem of value at this time.

TABLE 4.—BALLISTOCARDIOGRAPHIC STROKE VOLUME COMPARED WITH
1.73 Sq. M.

ESTIMATED STROKE VOLUME
1.73 Sq. M.

$$\left[S.V. = \left(46.12 \times \frac{C.E.}{Pm} \right) + 12 \right] \text{ and } \left[S.V. = \left(46.12 \times \frac{100}{Pm} \right) + 12 \right]$$

Case	Type of hypertension*	Mean arterial pressure, mm. Hg	% of normal heart size	Heart size Mean pressure	Observed stroke vol. per 1.73 sq. m.	Estimated stroke vol. C.E. Pm.	Stroke vol. estimated from Pm only	Sex
1	E	110	125	1.14	69	65	54	M
2	M	116	105	.90	37	53	52	M
3	E	117	100	.85	47	51	51	F
4	M	119	115	.96	57	56	51	M
5	E	121	100	.82	47	50	50	M
6	E	123	85	.69	40	44	49	F
7	E	124	87	.70	44	48	49	F
8	E	126	100	.79	49	48	48	M
9	E	127	100	.91	46	54	48	M
10	E	128	115	.82	51	50	48	F
11	E	128	105	.82	45	50	48	M
12	E	128	105	.82	39	42	48	F
13	E	128	85	.66	49	54	48	M
14	E	128	115	.90	51	45	48	M
15	E	128	93	.72	52	51	47	F
16	M	130	110	.85	49	49	47	M
17	E	131	105	.81	54	55	47	M
18	E	132	123	.94	49	50	47	M
19	E	133	110	.83	48	53	46	M
20	E	133	110	.83	56	53	45	M
21	E	135	120	.89	59	47	45	M
22	E	137	105	.88	51	53	45	F
23	E	138	125	.76	56	46	45	M
24	E	139	102	.90	45	54	44	M
25	E	140	130	.73	57	46	44	M
26	E	141	105	.92	40	48	44	M
27	E	143	110	.73	43	47	44	M
28	E	143	110	.77	43	53	44	M
29	E	144	128	.76	53	47	43	F
30	E	144	110	.89	44	53	43	M
31	E	144	110	.76	55	47	43	F
32	E	145	128	.88	43	50	43	M
33	E	145	110	.76	51	47	43	M
34	E	146	120	.82	43	50	43	M
35	E	146	110	.75	54	50	43	F
36	E	146	120	.82	58	53	43	M
37	E	147	120	.88	60	49	43	F
38	E	147	130	.82	53	45	42	M
39	E	147	120	.81	45	43	42	F
40	E	148	120	.71	40	46	42	M
41	E	148	105	.67	44	45	42	F
42	E	148	100	.74	42	45	42	M
43	E	149	110	.71	49	42	42	F
44	E	149	105	.83	49	49	42	M
45	E	150	125	.67	50	49	42	M
46	E	150	100	.79	44	50	42	F
47	E	152	120	.82	38	43	42	M
48	E	153	125	.68	39	48	42	M
49	E	154	105	.68	50	49	41	M
50	E	154	105	.77	51	48	41	M
51	E	155	120	.81	51	48	41	F
52	E	155	125	.77	49	43	41	M
53	E	156	120	.77	43	49	41	M
54	E	156	105	.67	51	44	41	M
55	E	157	105	.80	44	47	41	F
56	E	157	110	.70	46	44	41	M
57	E	158	120	.76	44	41	41	M
58	E	158	120	.69	44	49	40	M
59	E	159	110	.63	57	48	40	M
60	E	159	100	.80	55	48	40	M
61	E	159	128	.78	43	50	39	F
62	E	163	123	.79	59	42	39	M
63	E	165	130	.77	37	39	38	M
64	E	165	125	.82	39	44	38	M
65	E	165	110	.65	50	40	38	F
66	E	168	100	.59	44	41	38	M
67	E	168	120	.70	37	48	38	M
68	E	172	105	.63	49	38	38	F
69	E	174	110	.77	42	43	37	M
70	E	175	135	.57	40	39	37	F
71	E	176	100	.59	26	38	36	M
72	E	178	105	.67	28	40	36	F
73	E	178	120	.57	36	42	36	F
74	E	180	100	.58	44	38	35	M
75	E	181	105	.60	37	34	34	F
76	E	184	120	.65	56	37	36	F
77	E	185	105	.57	52	33	36	F
78	E	187	110	.52	33			M
79	E	194	105					
80	E	201	110					
81	E	211						

* E = Essential. M = Malignant.

Discussion. The broad problems in which the data in this communication are a small part consist in the search for a substance with physiologic properties consonant with those of a substance which might cause renal hypertension in animals and essential hypertension in man. Our studies were directed chiefly to the effects of angiotonin on the cardiac output and the contour of the ballistocardiographic tracing in normal man and a comparison of these with the pressor substances tyramine and methyl guanidine sulfate. These two drugs were selected among the many others because study of their effects on the arterioles of rabbit's ears demonstrates that they, in common with angiotonin—though to a much less degree—cause arteriolar constriction of a sort in which arterial pressure rises, but without appreciable reduction in blood flow to the tissues (Abell and Page¹). Since we observed similarity in the cardiodynamics as recorded by the ballistocardiograph of hypertensive patients and in normal subjects with hypertension elicited by injection of angiotonin, it seemed desirable to ascertain whether reduction in blood pressure by means of antipressor and, perhaps significantly, angiotonin neutralizing kidney extracts, caused reversal to a more normal status.

Tyramine increased stroke volume somewhat but greatly reduced the heart rate, resulting in slight reduction in cardiac output. Methyl guanidine decreased stroke volume as well as reducing the heart rate, resulting in sharp reduction of cardiac output. Both substances produced most disagreeable symptoms even when the blood pressure was only moderately elevated. Contrasting with this is the fact that angiotonin decreased stroke volume but with only very moderate decrease in heart rate and marked reduction of cardiac output. Despite sharp elevation in blood pressure symptoms ordinarily do not appear.

The effects of angiotonin on the cardiovascular system in human beings have been made the subject of careful inquiries by Wilkins and Duncan,³ and Bradley and Parker.² Both groups demonstrated reduction in cardiac output and increase in venous pressure. Bradley and Parker conclude that, since Roentgen ray studies failed to show cardiac dilatation, the failure of the heart to increase its size in the face of increased venous pressure is attributable to increased "cardiac tone." This conclusion was further supported by the observation of Lorber,⁵ and Hill and Andrus,⁴ that in isolated perfused hearts there is decrease in the diastolic volume when angiotonin is injected. On the other hand, Wilkins and Duncan found an increase in cardiac size and other evidences of "myocardial failure" in otherwise normal persons.

It cannot be decided with certainty from the data available whether the injection of angiotonin reproduces the cardiac changes observed in either experimental or spontaneous hypertension. The latter differs certainly in that venous pressure is not increased. It

may well be, however, that during the brief periods of angiotonin injection, time is not allowed for adaptation to occur.

As regards the decreased cardiac output, Starr has observed this, as measured by the ballistocardiograph, in a considerable number of patients with essential hypertension. Our own results in 81 hypertensive patients also show reduction in stroke volume, the average being 46.8 cc., with an average cardiac output of 2.14 liters per minute per square meter of body surface, as compared with 56.4 cc. and 2.28 liters per minute per square meter for 25 healthy, normotensive adults (Table 4). Cardiac output may be normal simply because the rate of the heart beat has increased.

Wilkins and Duncan⁹ point out that the hypertension associated with acute nephritis has great similarity to that elicited by angiotonin. Both are characterized by elevation of venous pressure. The similarities may be brought to the fore by the fact that both occur within a brief space of time.

Bradley and Parker² found the cardiac output reduced chiefly as the result of bradycardia with little change in stroke volume when single injections of angiotonin were given. Our results, on the other hand, suggest the importance of reduction in stroke volume and less so the bradycardia.

Evidence gained from study of the isolated perfused heart, while not directly transferable to intact animals, nevertheless, is of importance. Hill and Andrus⁴ found that angiotonin decreased coronary blood flow and increased the amplitude of the beat without any significant effect on the rate of cats' hearts. It augmented the output and the "arterial" pressure within the perfusion system; here, too, without influencing rate. They conclude that angiotonin causes direct stimulation of the myocardium and augmentation of the ventricular beat.

Lorber⁵ observed constriction of the coronary arteries, decrease in the diastolic volume and increase in oxygen consumption, external work and efficiency of the heart in the isolated cat's heart. The fact that the vasoconstrictor and efficiency-increasing properties of angiotonin disappear with about the same dose, suggests that if the substance is liberated *in vitro* in sufficient quantity to exert one effect, it will probably exert the other as well.

When arterial pressure is lowered as the result of administration of kidney extract definite increase in cardiac output occurs. It seems reasonable to suppose that this is in part due to the decreased head of pressure against which the heart must work to eject its blood, resulting in more complete emptying of the ventricles. Since venous pressure does not rise when the arterial pressure falls, it is doubtful that increased filling of the heart plays any important part.

It may be of interest to speculate on the factors which influence cardiac output in hypertensives. One of these is the size of the heart, a second, the efficiency of ejection and the economy of effort with

which this is performed, and a third, the resistance against which the heart must work to expel blood. In most hypertensives the size of the heart is increased, but how much of this increase is due to increased diastolic volume, to hypertrophy, or to both, is not known. It is probable that this increased size helps in maintaining the cardiac output against an increased head of pressure. The hypertensive heart utilizes its ejection energy just as economically, and oftentimes more economically, than does the normal heart according to results of Wright, Hallaran and Wiggers¹⁰ based on reconstruction of the ejection phase of intraventricular pressure from the subclavian pulse curve for contour and brachial arterial pressure. The surface area of the curve above the diastolic value divided by that beneath this area gives a quotient expressing the economy of ventricular effort during ejection. The resistance against which the heart works is obviously increased and is directly proportional to the mean arterial pressure.

We have attempted to correlate the stroke volume with the first and third of these factors, namely, cardiac enlargement and mean arterial pressure, in a group of hypertensive patients studied in the Lilly Clinic. We are only too well aware that even if a correlation could be arrived at, the result must be accepted with great reserve until the separate factors are proven to be measured with reasonable accuracy.

Cardiac enlargement (C.E.) is measured on the Roentgen ray film by the percentage deviation from the predicted normal established by Ungerleider and Clark.⁸ Figure 4, drawn from the study of 81 hypertensive patients, suggests that a correlation exists (coefficient 0.718) when stroke volume corrected to 1.73 sq. m. of body surface is plotted against the per cent of cardiac enlargement.

mean arterial pressure
It might thus be anticipated that the cardiac output in early hypertension with little cardiac enlargement would be comparatively low.

By means of regression equations it is possible to establish constants allowing formulation of the equation

$$S.V. = \left(46.12 \frac{C.E.}{P_m}\right) + 12$$

where S.V. = stroke volume corrected to 1.73 sq. m. of body surface, C.E. = percentage of normal cardiac size, and P_m = mean arterial pressure. Stroke volume as predicted from this formula corresponded fairly closely with that measured by the ballistocardiograph (Table 4). The mean deviation from the measured value was 12.5.

The most evident source of inaccuracy in the formula is the fact that the fraction $\frac{C.E.}{P_m}$ has only a small variation while the correction factor is large. Since the range of S.V. is also not great it can be questioned whether correlation between S.V. and $\frac{C.E.}{P_m}$ really exists.

If the observed P_m and S.V. values of Table 4 are arranged in descending order of P_m it is clearly seen that S.V. is inversely proportional to P_m . In short, as the pressure rises in hypertension, the stroke volume is decreased, which is what might be anticipated. If the factor of cardiac enlargement is added, the heart should perform its work against a higher resistance more capably and stroke volume fall off less than if cardiac enlargement were not included in the calculation. Of 81 determinations, the calculated value was closer to the observed when cardiac enlargement was included in the formula in 48 examples. In 10 examples, no difference would be anticipated as the heart size was normal, while in 23 the estimate was more accurate when it was omitted.

Starr, Donal, Margolies, Shaw, Collins and Gamble⁷ pointed out that hypertensives with small hearts have stroke volumes smaller than normal. Since they have shown that the basal work per beat of the normal heart is a function of its size, *i. e.*, an extension of Starling's Law of the Heart to clinical conditions, it is not surprising that a relationship between stroke volume and $\frac{C.E.}{P_m}$ might be found.

Summary. 1. The effect of angiotonin, tyramine and methyl guanidine on cardiac output was studied in 6 normotensive young adults by means of the ballistocardiograph. Tyramine increased stroke volume and greatly reduced heart rate, resulting in slight reduction of cardiac output. Methyl guanidine decreased stroke volume and rate, resulting in sharp reduction of cardiac output. Angiotonin decreased stroke volume but reduced the rate only slightly, resulting in marked reduction of cardiac output. Tyramine produces severe symptoms, methyl guanidine less severe ones, and angiotonin almost none at all.

2. The cardiodynamics, as recorded by the ballistocardiograph when tyramine and methyl guanidine are injected, differ strikingly from those of patients with essential hypertension or after injection of angiotonin into normotensives.

3. Antipressor angiotonin-destroying kidney extract administered to hypertensive patients elevated cardiac output when the mean arterial pressure fell and the contour of the ballistocardiographic curves resumed a normal or near normal appearance.

4. Stroke volume and cardiac output as measured by the ballistocardiograph are definitely reduced in many hypertensive patients.

5. An attempt has been made to relate by means of a formula stroke volume with cardiac enlargement and mean arterial pressure.

Conclusions. The cardiac effects of tyramine, and less so of methyl guanidine, as measured by the ballistocardiograph are such as to make it unlikely that they participate in the genesis of renal hypertension. On the contrary, angiotonin exhibits properties which are consonant with those anticipated from knowledge of the cardiodynamics in hypertension. This view is strengthened by the

observation that antipressor, angiotonin-destroying extracts of kidneys administered to hypertensive patients abolish at least one characteristic action of angiotonin, *i. e.*, they increase the depressed cardiac output.

We wish to express our appreciation to Drs. Stanley Bradley, Homer Smith and Isaac Starr for their aid in this investigation.

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THE EFFECT OF A HIGH-FAT TEST MEAL ON BLOOD CHOLESTEROL IN NORMAL AND OBESE INDIVIDUALS

By ELLIOT OPPENHEIM, M.D.

AND

MAURICE BRUGER, M.D.

With the technical assistance of SAMUEL MEMBER, B.S.

NEW YORK, N. Y.

(From the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University)

EXPERIMENTAL evidence to the effect that the cholesterol content of the blood in human subjects may be altered by the ingestion of a meal high in cholesterol or fat (or both) remains conflicting. Widal, Weill and Laudat²⁴ noted a marked increase in blood cholesterol in healthy subjects fasting for 15 hours and then given a meal consisting of meat, potatoes, bread and 50 gm. of butter. In 10 of 11 healthy individuals fed a meal consisting of soup, bread, meat, green vegetables, 2 eggs and wine, Rouzaud *et al.*¹⁹ found no increase in the blood cholesterol 4 to 5 hours after the meal. In one subject, an increase of 5% in the cholesterol content of the blood was observed. Luden¹⁶ noted that whereas the ingestion of bread, butter and tea had no effect on blood cholesterol, a heavier meal consisting of bread, butter, tea, 1 egg and $\frac{1}{2}$ cantaloupe produced an increase of 25 to 30%. Denis¹⁰ reported no increase in blood cholesterol in 3 subjects after a meal high in fat.

Hiller, Linder, Lundsgaard and Van Slyke,¹³ using a test meal consisting of butter (usually 1 gm. per kilogram) found no significant

increase in the whole blood or plasma cholesterol in 6 normal subjects and in 7 patients with nephritis. Bürger and Habs⁷ observed large increases in serum cholesterol (up to 100%) after the ingestion of 100 gm. of olive oil and 5 gm. of cholesterol. Barreda¹ and Snapper and Parisel²² utilizing the same diet were unable to confirm these results. Chaikoff, McGavack and Kaplan⁸ found no increase in the free or combined cholesterol of the blood in 6 of 7 subjects following the ingestion of 100 ml. of olive oil; 1 subject showed an increase of 35% in the total cholesterol content of the blood 4 hours after the meal. Gardner and Gainsborough¹² reported no increase in blood cholesterol following a single meal high in cholesterol. Bruger and Somach⁶ also observed that the ingestion of food had no appreciable effect either immediate or late on blood cholesterol.

Rony and Levy¹³ found no increase in the cholesterol content of the plasma in 8 normal and 18 obese subjects after the ingestion of a test meal consisting of 500 ml. of 20% cream. Using the same test meal, Blotner⁵ confirmed the lack of increase in blood cholesterol in normal persons but reported a marked rise in the blood cholesterol level in obese individuals. In subjects who were underweight, the blood cholesterol remained either unchanged or decreased. In patients with psoriasis and in non-dermatologic patients, LeWinn and Zugerman¹⁵ reported marked increases in the total blood cholesterol following a test meal high in fat.

In view of these conflicting observations, this problem (alimentary hypercholesterolemia) was reinvestigated.

Material and Methods. Seven normal subjects (laboratory technicians) ranging in weight within 10% of the calculated normal weight were placed on a low fat and low cholesterol diet* for 2 days. On the morning of the 3d day, a fasting specimen of blood was taken and again at intervals of 1½ hours for 6 hours. During this time, the subjects followed the prescribed diet and continued their usual activities. After this initial study, they remained on the low fat and low cholesterol diet for 2 more days. On the 6th day, a fasting specimen of blood was again taken and a test meal consisting of 500 ml. of cream (20% fat) was given. Blood specimens were taken again at intervals of 1½ hours for 6 hours. No food other than the test meal was permitted during this second phase of the experiment.

Thirteen subjects who were from 23% to 92% overweight were placed on the low fat and low cholesterol diet for 2 days. On the morning of the 3d day, a fasting specimen of blood was taken and the test meal given. Blood specimens were obtained at intervals of 1½ hours for a period of 6 hours.

The total and free cholesterol content of the serum was determined by the Schoenheimer and Sperry method²¹ as modified by Fitz¹¹ and adapted for the photoelectric colorimeter. In addition, the total cholesterol content of the whole blood, plasma and saline-washed red blood cells was determined by a modified Bloor procedure.^{17,20} The serum of 3 obese subjects was also analyzed for total lipids and fatty acids by the method of Bloor.⁴

* Milk, cottage cheese, lean beef, lamb, chicken or fish, clear broth, cooked cereals, white bread, potatoes, macaroni, noodles, rice, spaghetti, vegetables, fruits, gelatin, junket, coffee or tea.

TABLE 1.—VARIATIONS IN THE TOTAL AND FREE CHOLESTEROL CONTENT OF THE SERUM IN 7 NORMAL SUBJECTS ON A DIET LOW IN FAT AND CHOLESTEROL AND AFTER A TEST MEAL HIGH IN FAT

Subject			Age and sex			% over or under weight			Low fat and low cholesterol diet						High fat test meal											
									Total cholesterol* mg./100 cc.			Free cholesterol* % of total			Total cholesterol* mg./100 cc.			Free cholesterol* % of total								
Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	++	+	- +	Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.				
E. R.	20 F	0	200	200	184	188	190	0	8.0	26	25	25	25	25	194	194	192	199	207	8.2	1.0	31	28	28	28	27
E. F.	25 F	- 6	254	256	250	240	238	0.8	6.0	27	27	26	27	25	240	238	227	234	225	0	6.3	27	29	29	31	29
S. E.	24 F	+ 3	208	205	231	201	203	10.5	3.3	24	24	27	26	26	183	188	186	184	200	8.5	0	29	27	28	29	27
M. D.	27 M	+ 9	270	270	263	260	265	0	3.7	26	26	27	25	26	278	280	268	265	265	0.7	4.6	27	26	28	28	27
A. A.	24 F	- 10	180	186	178	194	176	7.8	2.3	27	25	25	24	25	175	195	188	170	182	10.8	2.8	28	28	29	30	29
A. H.	22 F	- 6	168	168	162	175	159	4.0	5.9	26	25	27	26	27	176	182	181	175	164	2.8	6.8	26	24	26	26	28
M. Mc.	22 F	- 4	157	160	145	160	161	2.5	7.6	24	24	25	24	25	159	158	158	151	151	0	5.0	23	24	24	27	27
Mean	205	206	202	203	199	3.8	5.3	26	25	26	25	26	201	205	200	197	199	4.4	3.8	27	27	27	28	28

* Method of Schoenheimer-Sperry.^{11,21}

† Per cent deviation from fasting level.

Results and Comments. In 7 subjects with normal body weight, the ingestion of a diet low in fat and cholesterol or a test meal high in fat failed to influence the total cholesterol content of the serum over a period of 6 hours (Table 1). On the low fat and low cholesterol diet, the maximal deviations from the fasting level of the total serum cholesterol ranged from +10.5% to -8% with a mean of +3.8% to -5.3%. On the high fat test meal, the maximal deviations ranged from +10.8% to -6.8% with a mean of +4.4% to -3.8%. The findings confirm the early observations of Bloor³ and Knudson¹⁴ in dogs but are at variance with some observations in humans.^{7,15,16,24} In two instances, the test meal high in fat resulted in a decrease rather than an increase in the total serum cholesterol; this phenomenon was previously described by Barreda¹ and Gardner and Gainsborough.¹² Table 1 also shows the remarkable constancy of the free cholesterol expressed as per cent of the total cholesterol on both dietary régimes, an observation previously recorded by Sperry.²³

TABLE 2.—VARIATIONS IN THE TOTAL AND FREE CHOLESTEROL CONTENT OF THE SERUM IN 13 FEMALE OBESE INDIVIDUALS AFTER A TEST MEAL HIGH IN FAT

Subject	Age	C ₂ Over- weight	Associated clinical conditions	Total cholesterol* mg./100 cc.								Free cholesterol* % of total					
				Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+†	-†	Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.		
J. M.	46	59	Synovitis left knee	207	200	219	194	200	5	8	6	3	26	26	25	28	27
M. G.	44	47	None	236	238	242	240	240	4	2	0	27	26	25	27	28	
Y. P.	49	65	None	236	214	227	230	242	2	5	9	7	28	27	26	27	26
R. C.	49	92	None	268	258	248	252	250	0	7	1	26	28	29	28	28	
S. P.	37	36	Hypertension	337	326	322	319	330	0	5	3	25	27	27	28	29	
N. W.	55	46	Hypertension	256	251	258	273	258	6	6	0	29	31	29	29	31	
M. S.	18	55	None	200	201	197	196	197	3	5	2	25	26	26	29	28	
R. L.	23	23	None	225	219	205	208	214	0	8	9	25	25	26	26	25	
M. F.	42	23	Varicose veins	320	312	304	320	329	2	8	5	0	27	26	27	26	25
E. G.	47	41	Phlebitis	254	263	268	261	263	5	5	0	27	27	27	27	28	
C. R.	33	26	None	273	270	273	263	286	4	8	3	28	28	28	28	27	
C. S.	49	39	None	273	270	258	265	283	3	7	5	5	25	26	27	27	27
E. H.	40	50	Varicose veins	205	205	205	210	217	5	9	0	26	25	27	25	27	
Mean	253	248	248	248	254	3	5	4	2	26	27	27	27	27

* Method of Schoenheimer and Sperry.^{11,21}

† Per cent deviation from fasting level.

In 13 obese women, the ingestion of a meal high in fat likewise was without effect on the total cholesterol content of the serum over a period of 6 hours (Table 2). The maximal deviations from the fasting level of the total serum cholesterol ranged from +6.6% to -9.7% with a mean of +3.5% to -4.2%. These findings failed to confirm those of Blotner⁵; he noted a marked increase in blood cholesterol in obese individuals following the ingestion of 500 ml. of 20% cream (the test meal used in this study). Of interest is the finding in this series that not only did the serum cholesterol fail to rise significantly after the high fat test meal but in 3 of the 13 observations, a decrease in serum cholesterol was demonstrated.

The constancy of the free cholesterol noted above was again observed.

In this study, 2 methods for the determination of blood cholesterol were used. Emphasis is placed on the Schoenheimer and Sperry method²¹ (Tables 1 and 2) since this procedure is conceded to be the most accurate colorimetric method available today for determining this constituent of the blood. However, since many of the published reports on this subject utilized the original² or a modified Bloor procedure,²⁰ this method was also employed in this investigation (Table 3). In general, the results obtained with both methods were similar, though greater individual variations in the total cholesterol were observed with the latter procedure. Table 3 shows that in subjects with normal or increased body weight, no significant alteration in the total cholesterol content of the whole blood, plasma and saline-washed red blood cells was observed after a test meal high in fat.

TABLE 3.—VARIATIONS IN THE CHOLESTEROL CONTENT OF WHOLE BLOOD, PLASMA AND SALINE-WASHED RED BLOOD CELLS IN 7 NORMAL SUBJECTS AND IN 13 OBESE INDIVIDUALS ON A DIET LOW IN FAT AND CHOLESTEROL AND AFTER A TEST MEAL HIGH IN FAT

(SUMMARY TABLE OF AVERAGE VALUES)

Experiment	Total cholesterol* mg./100 cc.					% deviation from fasting level	
	Fast- ing	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	+	-
Normal subjects							
Low fat and low cholesterol diet							
Whole blood	164	170	171	166	169	4.3	0
Plasma	166	165	162	163	166	0	2.4
Red blood cells	120	125	119	133	113	10.9	5.9
High fat test meal							
Whole blood	164	167	167	161	170	3.6	1.8
Plasma	166	165	164	167	165	0.6	1.2
Red blood cells	109	108	115	113	114	5.5	1.0
Obese subjects							
High fat test meal							
Whole blood	193	190	196	194	193	1.5	1.5
Plasma	196	193	190	192	197	0.5	3.1
Red blood cells	124	128	125	124	121	3.2	2.4

* Modified Bloor method.^{17,20}

In 3 obese individuals, it was further demonstrated (results not tabulated) that the ingestion of a test meal high in fat increased appreciably the total lipids and fatty acids in the serum as previously noted by Cowie and Hoag⁹ and Rony and Levy.¹⁸

Conclusions. 1. In subjects with normal body weight, the ingestion of a diet low in fat and cholesterol or a test meal high in fat (500 ml. of 20% cream) failed to alter the cholesterol content of the serum, whole blood, plasma and saline-washed red blood cells over a period of 6 hours.

2. In obese women, a test meal high in fat was followed by significant increases in the concentration of total lipids and fatty

acids in the serum but failed to influence the total cholesterol content of the serum, whole blood, plasma and saline-washed red blood cells.

3. The free cholesterol content of the serum expressed as per cent of the total cholesterol remained remarkably constant in normal and obese individuals on both dietary régimes.

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LEUKOCYTOSIS INDUCED BY METHYL-ACETAMIDE WITH P-CHLORO-XYLENOL

CHEMOTACTIC EFFECT ON BONE MARROW

BY BERNHARD ZONDEK, M.D.

PROFESSOR

AND

YEHUDA M. BROMBERG, M.D.

ASSISTANT

JERUSALEM, PALESTINE

(From the Gynecologic-Obstetric Department of the Rothschild Hadassah University Hospital and the Hormone Research Laboratory of the Hebrew University)

It is well known that bone marrow reacts to various chemical and biologic substances with the formation and liberation of leukocytes. This exaggerated activity is expressed by an increase in the number of leukocytes in the peripheral blood. Among the chemical substances possessing this property, nucleic acid and its derivatives (adenin and guanin) are the best known. Their employment in various leukopenic conditions, however, has given only transitory results, their effect being limited to the liberation of mature leukocytes but with no stimulus to their new formation. Furthermore,

leukocytosis resulting from the injections of nucleinic acid is preceded by a brief leukopenia, thus limiting its use in severe agranulocytosis. This undesirable effect is avoided by the use of pentose nucleotide.

Powers, Murphy and Humphreys² (1933) have described a leukocytosis provoked by injections of hepatic extract. This leukocytosis is of short duration and has given no results in the treatment of granulocytopenic conditions¹ (typhoid, agranulocytosis, and so forth).

Exogenic chemical substances, like collargol and pyrogallol, are also able to provoke leukocytosis in a normal individual, but have little effect in leukopenic conditions. These substances have not been introduced in therapeutics because their leukocytosis effect is often followed by periods of granulopenia due to inhibition of the leukopoietic function.

During investigations on the chemotherapeutic use of halogenized phenols (Zondek³), the solubility of p-chloro-xylenol in various substances was studied. Among these was methyl-acetamide,* which in contradistinction to other solvents, induced a distinct leukocytosis in the blood stream when injected intramuscularly.

Methyl-acetamide produced a leukocytosis of short duration, but the combination of methyl-acetamide with p-chloro-xylenol was found to prolong and strengthen considerably the leukopoietic effect. It should be mentioned that p-chloro-xylenol alone has no influence on the leukocytic function of bone marrow (Zondek³).

Methods. It is well known that the number of leukocytes in a normal individual undergoes important fluctuations during the day, being lowest about 11 A.M. and 11 P.M. and highest at about 5 A.M. and 5 P.M. In the normal individual more than 10,000 leukocytes were never found at any time.

The leukocytic counts were performed at fixed hours—11 A.M. and 6 P.M. The results are the average of at least two separate counts. The drug was regarded as producing a positive effect when the count rose to over 10,000. All physiologic factors influencing the number of circulating leukocytes were eliminated as far as possible. All persons examined were admitted to hospital, lay in bed and received a constant diet. Muscular effort was strictly forbidden. In each case the normal number of leukocytes was determined for several days, before beginning the treatment. The substances studied were administered at the same time of the day, to all subjects.

The following products were examined for their chemotactic effect:

1. A 70% solution of methyl-acetamide (referred to as "M").
2. A 70% solution of methyl-acetamide with 15% p-chloro-xylenol (referred to below as "15% CXM").
3. A 70% solution of methyl-acetamide with 25% p-chloro-xylenol (referred to below as "25% CXM").
4. A 10% solution of p-chloro-xylenol in oil.

The studies were performed on 25 persons, of whom 17 were normal, 4 suffered from typhoid fever with leukopenia, and 4 had local infections with leukocytosis.

* We are indebted to the Teva, Middle East Pharm. & Chem. Works, Ltd., Jerusalem, for their kind supply of methyl-acetamide and p-chloro-xylenol.

Studies in Normal Subjects. A. Leukopoietic Effect of Methylacetamide. Deep intramuscular injections of 10 cc. of methylacetamide, in the normal individual, produce after 24 hours a leukocytosis which is about 60% higher than the highest preceding

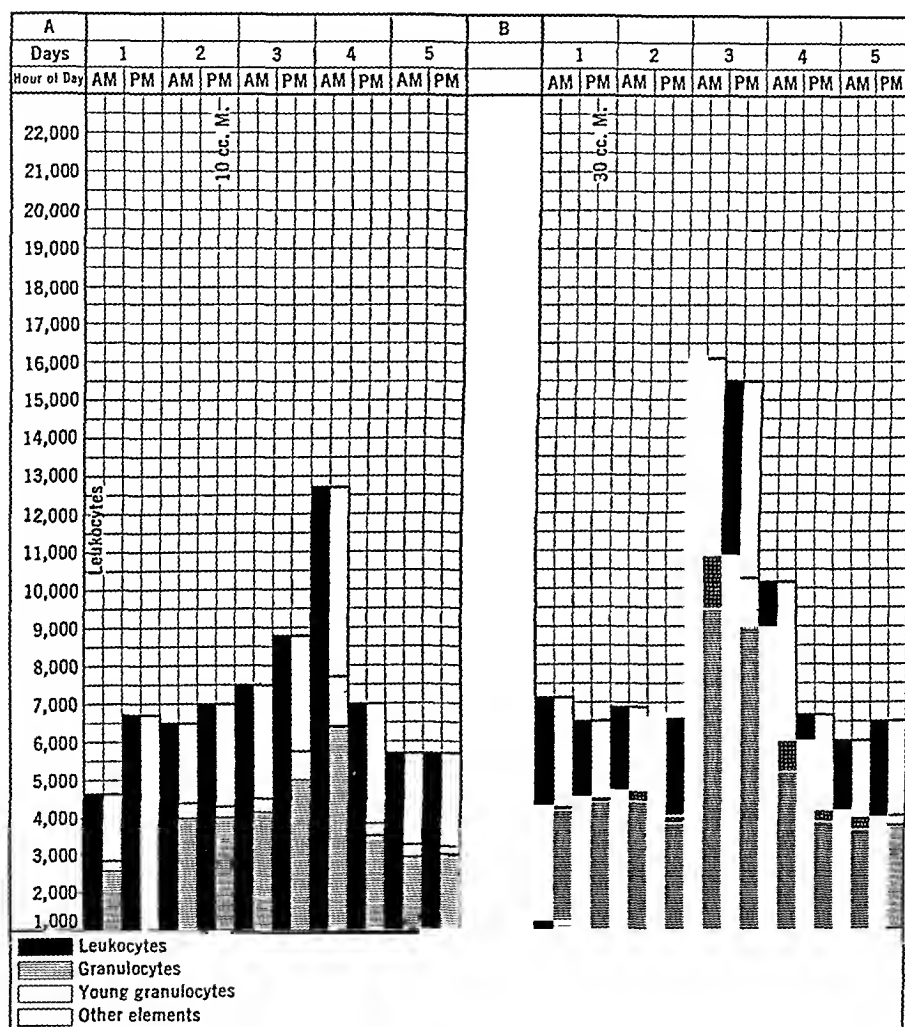


CHART 1.—Number and distribution of leukocytes after 10 cc. and 30 cc. of methylacetamide.

leukocyte count (Chart 1, A). This leukocytic reaction is in direct proportion to the dose of methylacetamide given: thus, 30 cc. of this substance have induced a leukocytosis of double the original number of leukocytes and of somewhat longer duration than do 10 cc. (Chart 1, B). This leukocytosis is due especially to an increase

in the number of younger forms of granulocytes. Methyl-acetamide alone, as a leukocytosis producing factor, is not suitable for practical purposes, because large doses are required to induce a prolonged leukocytosis.

B. *Leukopoietic Effect of Methyl-acetamide Combined with p-chloro-xyleneol*. Injections of 10 cc. methyl-acetamide with 15% p-chloro-xyleneol induce an increase in the number of leukocytes, 80% higher than the initial counts. This leukocytosis is due especially to the granulated elements, and reaches its maximum 48 hours after injection. Leukocytosis of similar character but still higher and more prolonged is obtained by injections of methyl-acetamide solutions with 25% p-chloro-xyleneol. Ten cubic centimeters of this product provoke a rise in the leukocytic count beginning 24 hours after injection, reaching the maximum (double the original number) after 48 hours and lasting for a further 48 hours.

The injection of 10% p-chloro-xyleneol in oil did not induce leukocytosis in normal individuals. On the other hand, it has been shown that the addition of p-chloro-xyleneol to methyl-acetamide (CXM) increases the latter's chemotactic effect on leukocytosis, which is stronger in proportion with the concentration of p-chloro-xyleneol.

It should be emphasized that the leukocytosis induced by these substances is not preceded by nor followed by leukopenia.

We attempted to produce a prolonged leukocytosis with methyl-acetamide in 25% p-chloro-xyleneol (25% CXM). Fifty cubic centimeters of this solution, given over 3 days, induced leukocytosis (over 10,000) of 10 days duration and with maximal counts of 20,200. This leukocytosis was due especially to the neutrophils which increased more than fourfold in absolute numbers, their proportion to the other white blood corpuscles increasing from 72 to 80%. In another case (Chart 2) 70 cc. of the same product (25% CXM), given over 3 days, caused a leukocytosis of 10 days duration, with an enormous rise in leukocytes reaching its maximum (30,200) on the 4th day after the beginning of injections.

Studies in Patients with Leukopenia. The effect of 25% CXM in leukopenic conditions was investigated in 4 typhoid cases (the only leukopenic conditions at our disposal).* The leukopenia in typhoid, which is due to the inhibition of the granulopoietic function of the bone marrow, is particularly resistant to chemotactic substances. In these cases also it was possible to induce leukocytosis with 25% CXM. Here, however, the antagonistic action of the bone marrow is indicated by the need for higher doses and the short duration of leukocytosis. A 7-year-old boy received 56 cc. of 25% CXM during 5 days, which increased the leukocyte count from 5000 to 12,000, the increase of neutrophils paralleling that of the leukocytes.

* We are indebted to Dr. Gruenfelder, Head of the Pediatric Department, for putting these cases at our disposal.

In another case, a 10-year-old boy, the rather high dose of 72 cc. of 25% CXM given over 5 days, induced a neutrophilic leukocytosis, reaching a maximum of 32,400 on the 5th and 6th day after beginning of treatment (Chart 3). The leukocytic count, however, had dropped to the initial level 36 hours after stopping treatment.

In normal patients whose bone marrow is not depressed as it is in typhoid fever, the increased leukocyte count persists for about 10 days.

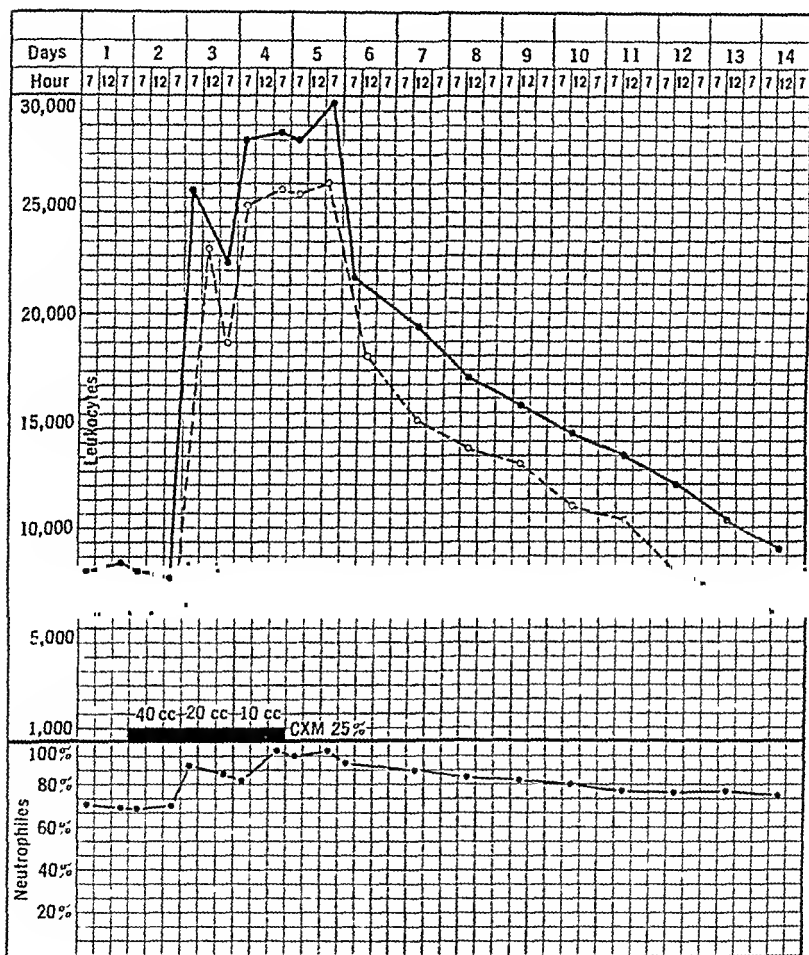


CHART 2.—Leukocyte changes after 70 cc. of 25% CXM.

Studies in Patients with Leukocytosis. In cases of inflammatory conditions with leukocytosis the response to methyl-acetamide seems to be more prompt than in normal conditions. For instance, a case of pyelitis with a count of 9200 reacted to injection of 25% CXM with a leukocytosis of 38,000.

Qualitative Changes in the Leukocytic Picture Induced by CXM Treatment. It is well known that an increase in neutrophils in the peripheral circulation is due to their increased production in the bone marrow. Nevertheless, this rule is subject to certain exceptions. Thus, the spleen is thought to be able, in certain conditions, to accumulate or liberate leukocytes with resulting phases of leuko-

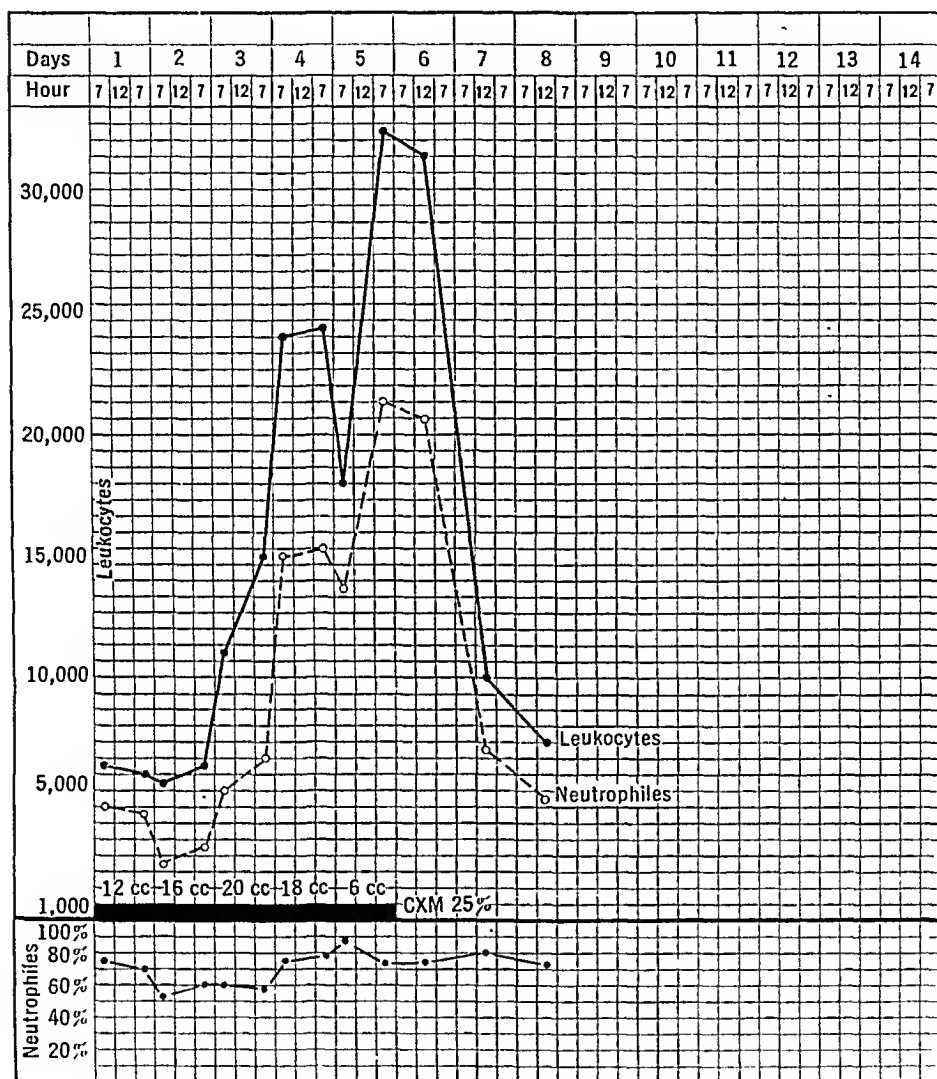


CHART 3.—Leukocytosis produced by CXM in typhoid leukopenia.

penia and leukocytosis (leukocytosis due to redistribution). In order to determine whether the leukocytosis obtained after the injection of CXM was due to redistribution or to direct stimulation of the bone marrow, the qualitative study of the neutrophils was necessary. In the former case the white differential count is that of normal blood, while in the latter the young cells driven from the center to the peripheral blood shift the differential count to the left.

CXM, when given in sufficient quantities, induces leukocytosis with a clear shift to the left. This occurred in all 25 cases. As an example, the Schilling's hemogram of 1 case is reported below (Table 1). The leukocytosis rises from 9200 up to 38,000. The qualitative blood study reveals a distinct shift to the left. The number of young and band forms increased, while the myelocytes were not found in the peripheric blood.

TABLE 1.—LEUKOCYTOSIS WITH SHIFT TO THE LEFT INDUCED BY CXM

	Before treatment	After treatment with 70 cc. of 25% CXM
Leukocytes	9,200	38,000
Basophils		
Eosinophils	1	
Neutrophils:		
Myelocytes		
Young forms	..	3
Band forms	1	13
Segment	79	62
Lymphocytes	17	14
Monocytes	1	1

The number of young forms of neutrophils in circulation permits the evaluation of the effect of CXM on bone marrow. The age of neutrophils was determined according to Arneth's method, where the ratio between the monolobar and segmented neutrophils (nuclear shift index) is proportional to the extent of bone marrow stimulation by the substance used. Following treatment with large doses of CXM, the shift index, which is normally 6.2% (according to Schilling) was found to be about 25%.

In some cases, following excessively high doses of CXM, we found neutrophils with pyknotic nuclei or toxic granulated protoplasm—which might have suggested a degenerative process of the bone marrow. The sternal puncture performed during the peak of leukocytosis revealed a high percentage of band forms.

CXM was found to stimulate electively the granulopoietic function of the bone marrow, not affecting the other elements of the white series, erythropoiesis or thrombocytopoiesis. The strong and elective effect of CXM on the granulopoietic function of bone marrow allows one to expect favorable results in the treatment of neutropenic conditions. Moreover, CXM has the advantage of combining its chemotactic effect with the chemotherapeutic properties of p-chloro-xylene (Zondek³). CXM may thus be indicated in cases of agranulocytosis secondary to general infection.

Studies in Animals. The chemotactic effect of CXM was studied in rats, hens and rabbits. The considerable fluctuations in the number of leukocytes in normal conditions in these animals make it difficult to reach any definite conclusion in these experiments. In hens, the leukocytes rose from 60,000 to 80,000 after 3 cc. of 25% CXM given during 6 days. In the rabbit the leukocytic count rose from 9000 to 13,000 following 10 cc. of 25% CXM given during

11 days. Nevertheless, the leukocytic level did not surpass that which is found in normal conditions.

Toxicity. The lethal dose of a 70% solution of methyl-acetamide (M) in mice weighing 16 gm. was found to be 0.2 cc., while the corresponding dose of 25% CXM was 0.1 cc. Rats weighing about 100 gm. show no disturbances after administration of 0.5 cc. of 25% CXM. Rabbits weighing 1100 to 1200 gm. can stand 1 cc. of 25% CXM daily, even when given for 10 days or more. In men, the highest dose which causes no complaints was 20 cc. 25% CXM daily (2×10 cc. daily). Higher doses cause local and general disturbances. Locally, we sometimes observed tissue necrosis and neuritis. Vomiting, probably of central origin, was also observed, following large doses. It should be emphasized that vomiting coincided with high leukocytic levels.

Dosage. The dose of 25% CXM necessary to induce a strong leukocytic reaction in men is: 2 injections of 10 cc. of 25% CXM during the first day and 1 injection of 10 cc. daily for the next 3 days. In order to avoid infiltrative reactions and discomfort, these injections should be given intragluteally in the deeper muscular layers and 2% anesthesin should be added.

Summary and Conclusions. 1. The chemotactic effect of methyl-acetamide alone and combined with p-chloro-xyleneol was studied in 25 patients.

2. Methyl-acetamide injected intramuscularly induces leukocytosis, which reaches its maximum 24 hours after injection. This effect on leukopoiesis is proportional to the dose employed.

3. The injection of methyl-acetamide combined with p-chloro-xyleneol (CXM) gives a much higher leukocytosis than that of methyl-acetamide alone. The leukocytic effect produced is proportional to the quantity of p-chloro-xyleneol dissolved in methyl-acetamide.

4. In all the 4 cases of leukopenia in typhoid fever treated with injections of CXM, leukocytosis was induced.

5. The characteristic features of the leukocytosis produced by CXM are the shift to the left, with a significant increase in young and band forms. This supports the assumption that this leukocytosis is due to a stimulation of the granulopoietic function of bone marrow.

6. The results obtained in normal and in typhoid cases suggest the trial of these substances in neutropenic conditions.*

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* We have awaited a potent leukopoietic bone marrow stimulant ever since the leukopenic effect of mustard gas was demonstrated in World War I. We hope that the above study may start the solution of this problem.—ED.

LIVER FUNCTION IN THERAPEUTIC MALARIA*

BY ISRAEL KOPP, M.D.

RESEARCH ASSOCIATE, MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH,

AND

HARRY C. SOLOMON, M.D.

CLINICAL PROFESSOR OF PSYCHIATRY, HARVARD MEDICAL SCHOOL; CHIEF, THERAPEUTIC
RESEARCH, BOSTON PSYCHOPATHIC HOSPITAL,
BOSTON, MASS.

(From the Boston Psychopathic Hospital)

VARIOUS effects of malarial infections upon the liver have been observed. As measured by the levulose²¹ and galactose¹⁹ tolerance tests, glycogenetic function is lowered. Changes in the blood lipoids¹¹ and serum proteins¹² and increased hemoglobin catabolism with bilirubin formation may also affect liver function. Clifford¹ has maintained that the liver is permanently damaged as a result of malarial infections.

Enlargement and slight tenderness of the liver are often present in naturally acquired malaria^{18a} but has rarely been seen in therapeutic malaria. Clinical manifestations of liver involvement include icterus of a mild degree, bile-tinged vomitus, diarrhea, painful swelling of the liver, and dark-colored urine.¹⁷ The liver is always enlarged and congested when death is due to malaria.¹ Histologic evidence of damage to the parenchymatous cells of the liver in fatal cases is not uniform, but both degenerative changes and fat infiltration are sometimes found.^{14b} Cirrhosis of the liver is rarely seen. The duration of the primary disease and other concomitant circumstances play some part. Thus, malarial cirrhosis is frequent in southern Italy; whereas in other parts of the world and tropics it is rare.¹⁷

Icterus of the conjunctivæ occurs often in malaria, in 18 of 53 cases,³ but it is not of serious import, both in our experience and that of others. The icterus has been attributed to the rapid destruction of the red blood cells, a hemolytic jaundice, and not to biliary obstruction. The icterus of the conjunctivæ may become more intense as the paroxysms recur only to disappear with continuation of fever. Jaundice of the skin, however, is considered a more serious and dangerous sign,^{18b} and has necessitated immediate termination of the malaria. Jaundice is seldom seen during the first week or 10 days of the clinical attack, and is noted usually in patients in whom a high degree of parasitization of the red blood cells has produced a rapid and extreme anemia, 2 million or less, usually in 7 to 10 days.²²

Malarial therapy has been administered in this clinic during the past 17 years to approximately 400 patients because of syphilitic

* This study was made possible by a grant from Merck & Co.

infections of the nervous system. Generalized jaundice has been occasionally seen but has rapidly cleared with the cessation of the malaria. In a recent study of the effects of long-continued administration of tryparsamide upon the liver, it was necessary to determine the effect of malaria *per se* upon liver function. In the present communication, we wish to report observations of the effect of malaria upon the liver function of 9 patients.

Material. Nine male patients, ranging in age from 32 to 55 years, were hospitalized for the malarial therapy of general paresis. Prior to malaria the physical and laboratory examinations revealed no significant pathology other than that of general paresis. Six of the patients had received no chemotherapy prior to malaria. The remaining 3 had received trivalent and pentavalent arsenicals.

Methods. The patient was inoculated with tertian malaria. After an incubation period ranging from 3 to 7 days, fever resulted and was usually of the quotidian or mixed type. The patients were allowed from 4 to 12 paroxysms. The malaria was then terminated by the administration of quinine sulphate, 30 gr. daily, for 1 week. During the malaria treatment, attempts were made to maintain the nutrition of the patients though food intake was in some instances voluntarily reduced. Following malaria, the patient was placed on a high caloric and vitamin diet and ferrous sulphate, 20 gr. daily.

Liver function was determined before and after malarial therapy by the following procedures: 1, bromsulphthalein dye test; 2, cholesterol, total, free, and ester; 3, phospholipids; 4, hippuric acid excretion; 5, cephalin cholesterol flocculation test of Hanger; 6, fibrinogen; 7, total bilirubin; 8, van den Bergh reaction; 9, icteric index.

The bromsulphthalein dye test was at first fractionated, 2, 5, 15 and 30 minute samples being taken following the injection of 2 mg. of the dye per kilogram of body weight. Subsequently, only 18 and 30 minute samples were obtained since MacDonald¹³ has shown that 18 and not 30 minutes are required for complete removal of the dye in normal cases. The bromsulphthalein dye test is generally recognized as the most delicate index for the presence of liver disease in the absence of jaundice. Variations in hydration and kidney diseases do not affect the test. Congestive heart failure, however, makes the results unreliable.

Total cholesterol was determined on serum by a modification of the method of Bloor^{2a} and the free and ester cholesterol by a modification of the technique of Schoenheimer and Sperry.²⁰ Total cholesterol values of 150 to 230 mg. per 100 cc., a free percentage of 23% to 31%, and an ester percentage of 69% to 77% were considered normal. A fall in cholesterol ester percentage is usually considered a serious sign and is found only in the presence of infection or liver disease.^{24a} High ester values indicate a mild disturbance. Cholesterol metabolism may not be disturbed in the presence of considerable liver injury. Normal findings, therefore, do not rule out liver disease.

Phospholipid determinations were done on plasma following the lipid extraction technique of Bloor^{2b} and the digestion method and phosphate determination of Fiske and Subbarow.⁸ The normal range is from 8 to 9 mg. per 100 cc. Moderately reduced phospholipid values occur during the course of acute hepatitis.^{24b} Increased values, from 14 to 27 mg. per 100 cc. have been found during acute infections and toxic hepatitis (arsenic, etc.).

Hippuric acid excretion was determined by the Weichselbaum-Probstein²³ modification of the technique of Quick. An excretion of 4 gm. or more

over a 4 hour period following the oral ingestion of 5.9 gm. of sodium benzoate was considered normal. The hippuric acid excretion test is positive in all types of liver disease.²⁴ It can usually be correlated with the extent of liver damage, though normal findings may be obtained when liver damage is mild. The test is somewhat more reliable than the cholesterol ester percentage in the prognosis of cases of acute liver disease and far more reliable in the chronic cases of cirrhosis. It is helpful in prognosis since it invariably gives low results in severe and fatal cases. The hippuric acid excretion is altered in marked diminution of renal function.¹⁶ The test was considered significant in our patients only when normal kidney function by dye excretion was present.

The cephalin-cholesterol flocculation test was carried out according to the technique of Hanger.¹⁰ The cephalin-cholesterol antigen, dehydrated, was supplied by the Difco Laboratories, Detroit, Mich. The test was performed on freshly drawn blood serum and a control test was run on normal serum on every occasion. Readings were made at the end of 24 and 48 hours, no test being considered negative until 48 hours had elapsed.

Cephalin cholesterol emulsions are not usually flocculated by normal human serum, nor by serum from patients with obstructive jaundice.¹⁰ They are unaffected by the red cell sedimentation rate or by the Wassermann reaction. A negative flocculation has also been obtained on patients with hemolytic jaundice. Cephalin cholesterol emulsions are flocculated by serum from patients with active disturbances of liver parenchyma.¹⁰ The test serves as a means of distinguishing obstructive from hepatogenous jaundice. It does not parallel other liver function tests. Hanger has stated that the test is a more sensitive and accurate index of active disturbance of liver parenchyma than any of the liver function tests.

Fibrinogen was determined by precipitation as fibrin by the method of Cullen and Van Slyke,⁵ and the nitrogen content of the fibrin determined directly. Potassium oxalate, 2 mg. per 100 cc. was used as the anticoagulant. The usual limits of normal are from 190 to 330 mg. per 100 cc.⁹ Moderate liver damage itself is a stimulus to fibrinogen production. With more extensive destruction of the liver a failure of fibrinogen response occurs. Bilirubin was determined by a modification of the van den Bergh technique.¹⁶ Values of 0.8 mg. per 100 cc. or less were considered normal.

Results. Liver function tests before malaria were essentially normal in 8 of the 9 patients, except for the following: 4 patients showed slight bromsulphthalein retention (5% to 10%) at 18 minutes; and 5 patients revealed high fibrinogen values, from 340 to 540 mg. per 100 cc. These findings are not uncommon in patients with neurosyphilis prior to any type of therapy. Six of the 8 patients coöperated for the hippuric acid excretion tests which were normal. The ninth patient (J. T.), who had received intensive arsenical treatment over a 14-year period and had experienced a toxic hepatitis due to arsenic in 1928, revealed abnormal liver function tests; bromsulphthalein retention of 25% at 18 minutes and 10% at 30 minutes; lowered phospholipid values of 7.3 mg. per 100 cc. and a diminished hippuric acid excretion of 2.7 gm. (Table 1). The administration of malaria causes marked changes in liver function as revealed by moderate bromsulphthalein retention, a marked fall in total cholesterol and cholesterol ester values, diminished hippuric acid excretion, and a strongly positive cephalin flocculation test (Tables 1 and 2). The degree of liver function impair-

TABLE 1.—EFFECT OF ADMINISTRATION OF MALARIA ON LIVER FUNCTION TESTS

Name. Age.	Date.	Minutes 2-5-15-18-30 Bromsulphalein retention.	Cholesterol.		Cephalin flocculation.	Hippuric acid excretion, gm. 100 cc.	Fibrino- gen, mg. per 100 cc.	Phospho- lipids, mg. per 100 cc.	Bilirubin.	Van den Bergh.		Icteric index.	Hours fever above 100° (R).	Parox- ysms.	Trypar- samide, gm.	Malaria. 12-16-41 to 1-9-42
			Total mg. %.	Ester, %.						Indirect	Direct					
J. B. 44	12-15-41	163	200	66	0	5.65	300	8.2	Normal	Indirect	Indirect	6	132	7		12-16-41 to 1-9-42
	1-2-42	155	128	61	+++	4.58	280	7.6	Normal	Indirect	Indirect	6	179	11		
	1-22-42	153	162	69	+		330	8.0	Normal	Indirect	Indirect	5			1½	
	3-3-42				=											
A. C. 55	10-16-41	105	293	72	0		340	9.1	Normal	Indirect	Indirect	5				5 typhoid vac- cine fevers, 10-27 to 11-5-41
	11-10-41	111	284	67	+++		390	9.3	Normal	Indirect	Indirect	5	23		1½	
	12-1-41	105½	203	55	+++		410	9.4	Normal	Indirect	Indirect	4	112	9		11-7 to 11-27-41
	12-30-41	110	244	67	+		510	10.6	Normal	Indirect	Indirect	5			+3½ +8	9-9 to 10-1-41
	1-13-42				=											
W. D. 51	9-5-41	157	166	70	0	5.75	290	8.4	Normal	Indirect	Indirect	4	160	11		9-18 to 9-29-41
	10-6-41	142	188	66	+++	5.04	270	8.3	Normal	Indirect	Indirect	4				
	10-21-41	163½	234	70	++	5.55	300	8.9	Normal	Indirect	Indirect	5			1½	
	9-5-41	146½	163	71	0	4.87	350	8.1	Normal	Indirect	Indirect	6				
A. E. 32	10-2-41	142	119	31	+++	3.05	260	7.5	1 mg.	Indirect	Indirect	9	132	8		
	10-9-41	144	207	63	+++	2.97	350	8.0	Normal	Indirect	Indirect	6			½	
	10-23-41	145	204	66	+	4.58	320	8.1	Normal	Indirect	Indirect	8			+3 +23	
	1-15-42	155½	206	69	=	4.52	290	9.4	Normal	Indirect	Indirect	5			+9	
	2-10-42				0											
T. F. 39	9-15-41	185	211	73	0	5.63	320	8.1	Normal	Indirect	Indirect	3	139	11		9-22 to 10-16-41
	10-15-41	176½	116	60	+++	1.45	350	7.9	Normal	Indirect	Indirect	6				
	10-27-41	181	183	68	++	3.51	260	9.3	Normal	Indirect	Indirect	3				
	11-24-41	199	178	69	0	4.77	270	8.7	Normal	Indirect	Indirect	4			5	
M. G. 32	2-9-42	146	210	74	0	4.23	250	8.6	Normal	Indirect	Indirect	5				2-9 to 3-5-41
	2-17-42				0								86	3		
	2-19-42	133½			0								95	4		
	3-2-42				+++		310	6.9	Normal	Indirect	Indirect	6	159	11		
G. T. 39	3-5-42		70	10	+++	3.12			Normal	Indirect	Indirect	5	164	12		
	1-22-41	151½	76	30	+++	5.64	540	8.6	Normal	Indirect	Indirect	6				1-20 to 2-9-42
	1-27-41		258	72	0				Normal	Indirect	Indirect		40	2		
	1-29-41				0								72	3		
	2-4-41	145½			+++	5.3	290	7.8	Normal	Indirect	Indirect	6	103	6		
	2-13-41		111	50	=				Normal	Indirect	Indirect		135	10		
J. T. 55	2-17-41	140½			+											
	3-2-41		207	71	0		620	8.0	Normal	Indirect	Indirect	4				9-25 to 10-13-41
	9-10-41	134½	222	74	0	1.80	310	7.3	Normal	Indirect	Indirect	7	110	7		
	10-1-41	125	102	35	+++	1.50	300	7.0	2.4 mg.	Biphasic	Biphasic	15				
	10-27-41	126	214	71	+	1.48	280	8.1	Normal	Indirect	Indirect	7				
	11-24-41	136½	191	69	0	2.78	250	8.4	Normal	Indirect	Indirect	6			3½ +8 +8	
H. Y. 53	12-22-41	141	268	74	0		280	9.6	Normal	Indirect	Indirect	6				
	1-13-42		220	69					Normal	Indirect	Indirect	6				
	11-21-41	137½	205	73	0		470	8.7	Normal	Indirect	Indirect	5	73	4		11-26 to 12-5-41
	12-10-41	124½	160	57	+++		260	7.2	1 mg.	Indirect	Indirect	8				
	12-30-41	121	187	65	0		430	9.2	Normal	Indirect	Indirect	6			1	

ment did not appear to depend on the number of paroxysms, the total number of hours of fever above 100° (R), or the duration of active malaria. One patient (W. D.), aged 51 years, experienced 11 paroxysms and a total of 160 hours of fever above 100° (R) over a 19 day period. The liver function tests following the termination of the malaria were practically unchanged except for a +++ cephalin flocculation. On the other hand, a second patient (M. G.), aged 32 years, who experienced a similar number of paroxysms and fever over a 17 day period, showed marked changes in the liver function tests, a marked drop in the total cholesterol and cholesterol ester values, moderate bromsulphthalein retention, reduced hippuric acid excretion, lowered phospholipid values, and a +++ cephalin flocculation test (Table 1).

TABLE 2.—EFFECT OF MALARIA UPON LIVER FUNCTION.

	Normal range.	Before malaria.*	After malaria.
<i>Bromsulphthalein retention:</i>			
18 minutes, %	0	3 5	9 4
30 minutes, %	0	0	0
Fibrinogen, mg.	190-330	367 8	303 3
<i>Cholesterol:</i>			
Total mg. per 100 cc.	140-230	219	126
Free, %	69-77	71 1	47 2
Cephalin flocculation	0	0	+++
Phospholipids, mg.	8-9	8 25	7 53
Hippuric acid secretion, gm. . .	4-6	4 9	3 5

* Based on average values of 8 patients.

Patient who developed jaundice omitted.

Each of the 9 patients showed a strongly positive cephalin flocculation test as a result of malaria. In 1 of the group (patient A. C.), a negative flocculation test was present before fever therapy, became +++ positive after 5 mild fevers induced by typhoid vaccine and ++++ after malaria. Each patient also experienced a fall in the cholesterol ester percentage. Initial ester percentages before malaria were normal and ranged from 66% to 74%. Values obtained after malaria ranged from 10% to 66% and were abnormal in 8 patients. Total cholesterol values showed a marked reduction from an initial range of 163 to 284 mg. to levels of 70 to 203 mg. In 1 instance (M. G.), the total cholesterol fell from 210 to 70 mg.

Hippuric acid excretion was examined in 7 of the 9 patients following malaria; in each a reduction occurred, and in 3 of the 7 the results were below normal levels. In a fourth patient (J. T.), hippuric acid excretion, below normal before malaria, was still further reduced.

Bromsulphthalein retention of a moderate degree and greater than that present before fever occurred in 6 of the 9 patients. Phospholipid values decreased only slightly in 8 patients. Fibrinogen was increased in 3 patients and diminished in 6, but remained within normal limits in the latter group.

Patient J. T. (Table 1), who had presented evidence of impaired liver function prior to malaria, developed generalized jaundice after 7 paroxysms and the malaria was terminated. A marked fall in total cholesterol and cholesterol esters occurred. The cephalin flocculation test became ++++ positive.

The termination of malaria by quinine was followed by a rapid return of the liver function tests to normal in 3 to 6 weeks' time with the exception of the fibrinogen and cephalin flocculation tests. In 3 of 8 patients, fibrinogen remained increased. The cephalin flocculation test was the last as a rule to revert to normal. The test became negative in 2 patients (H. Y. and G. T.) 21 and 25 days after quinine therapy was started. Tryparsamide, from 0.5 to 36 gm., had been administered to the remaining 7 patients, and the cephalin flocculation test in this group required as long as 19 weeks to return to normal. Liver function tests returned to normal levels fairly rapidly even in the patient who had developed jaundice (J. T.) and to whom tryparsamide had also been given.

Liver function tests, except for the cephalin flocculation, were obtained only after malarial therapy on a second group of 5 patients, and 2 to 9 days after the administration of quinine. The findings were as follows: 3 patients revealed normal liver function tests with the exception of an increased fibrinogen in 1. Of the remaining 2 patients, 1 developed jaundice and revealed the following 2 days after malaria was terminated: an icteric index of 15, bilirubin, 2 mg. per 100 cc., a biphasic van den Bergh, bromsulphthalein retention of 15% at 15 minutes, cholesterol esters 52%, and a moderately diminished hippuric acid excretion. The fifth patient, nine days after quinine, revealed diminished phospholipid values and a significantly diminished hippuric acid excretion.

Discussion. Malarial therapy produces disturbances in liver function which are, however, of a transient nature. The outstanding findings on our patients were the marked reduction in total cholesterol and cholesterol ester percentages, the fall in hippuric acid excretion and the strongly positive cephalin flocculation tests. Less marked were the phospholipid reduction, bromsulphthalein retention and the quantitative and qualitative bilirubin changes.

The findings obtained on patient J. T., who developed generalized jaundice during malarial therapy, indicate that the jaundice of malaria is due to liver damage. The presence of liver pathology in this patient prior to the administration of malaria and probably as a result of prolonged arsenical therapy and a previous toxic hepatitis may be an important factor. A second patient (A. E.), who revealed nearly similar abnormal function tests as a result of malaria, experienced no jaundice. Liver function in this patient prior to malaria was, however, normal.

The findings of impaired liver function in 3 patients during malarial fever and before quinine therapy would indicate that this drug

per se was not a responsible factor. This conclusion is strengthened by the fact that improvement in liver function occurred even during the administration of quinine. The rapidly induced hemolytic anemia of malaria resulting in excessive bilirubin production does not impair liver function since it has been shown that intravascular hemolysis of red blood cells as produced by autohemolysins does not result in abnormal liver function tests.⁶ Liver function also is not impaired in the presence of a secondary anemia as occurs in malaria.⁶

Recently it has been shown that impairment of liver function occurs in protein-depleted animals.⁷ The production of hypoalbuminemia by restriction of food intake in animals produced an increasing fall in protein content of the liver and histologic changes such as loss of stainable cytoplasm. Rapid and progressive hypoalbuminemia has been observed in malaria.¹² It is possible that impairment of liver function in malaria may be due to the marked reduction in the serum albumin with depletion of the proteins in the liver. Termination of the malaria causes a rise in serum albumin to its pre-febrile level, usually within 10 to 24 days. Normal liver function tests were obtained on our patients after malaria at a time when serum albumin is rapidly returning to normal levels.

Of some interest in the treatment of neurosyphilis is the occasional appearance of jaundice after malarial fever is terminated and following the administration of the first few injections of an arsenical. It is possible that the administration of arsenicals after malaria and before liver function has returned to normal may overburden the liver and result in jaundice. The danger is probably less with pentavalent arsenicals (tryparsamide), little of which is found in the liver after administration than with trivalent arsenicals (neoarsphenamine, mapharsen, arsphenamine), a considerable portion of which is excreted by the liver.

Summary. 1. Tertian malaria was administered to 9 male patients for the treatment of general paresis and liver function determined before and after therapy.

2. Malaria produces disturbances in liver function as revealed by moderate bromsulphthalein retention, a marked reduction in cholesterol and cholesterol esters, a moderate fall in the phospholipids, diminished hippuric acid excretion and a strongly positive cephalin flocculation test.

3. The impairment of liver function is transient and clears usually within 3 to 6 weeks after termination of the malaria. The cephalin flocculation test is the last to revert to normal.

4. The administration of pentavalent arsenic in the form of tryparsamide immediately after malaria did not seem to delay the return of liver function tests to normal with the exception of the cephalin flocculation.

5. The occasional appearance of jaundice after malaria has been terminated and following the administration of the first few injec-

tions of an arsenical may be due to the residual hepatic damage of the former and the superimposed toxic effect of the drug.

The technical procedures were carried out by Miss Mabel Miller.

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CLINICAL EXPERIENCE WITH A WATER SOLUBLE VITAMIN K-LIKE SUBSTANCE

(TETRASODIUM 2-METHYL-1, 4-NAPHTHOHYDROQUINONE DIPHOS-
PHORIC ACID ESTER)*†

BY J. GARROTT ALLEN, M.D.

CHICAGO, ILL.

(From the Department of Surgery of The University of Chicago)

ALTHOUGH it has been almost 15 years since Dam^{5,6,7,8} began his classic experiments leading to the discovery of the fat soluble vitamin K, the clinical progress made with this important substance and its derivatives had been quite slow until 1939, when it was

* Synkayvite "Roche."

† This work was aided by grants from the Douglas Smith Foundation for Medical Research, and Hoffmann-La Roche, Inc., Nutley, N. J.

shown that the activity of this vitamin was dependent upon its quinoid structure.¹³ Many quinone derivatives were then studied for their antihemorrhagic activity, 2-methyl-1, 4-naphthoquinone being the first to be investigated in man. However this quinone and many of the others similarly studied are only very slightly soluble in water but freely soluble in most fat solvents. Therefore when orally administered, bile salts must of necessity be concomitantly given, or the preparation must be administered intramuscularly in oil. Thus its adaptability for general clinical use is limited.

The need for a water soluble vitamin K preparation suitable for oral, intramuscular or intravenous use has resulted in the synthesis of several compounds suitable for such purposes. Among the latter is the tetrasodium salt of the diphosphoric acid ester of 2-methyl-1, 4-naphthohydroquinone (Synkayvite), which has been found to possess an antihemorrhagic activity even greater than the fat soluble menadione (2-methyl-1, 4-naphthoquinone) when compared on an equimolecular basis.^{4,9,11}

It is the purpose of this report to present data obtained on patients with hypoprothrombinemia to whom vitamin K therapy in the form of water soluble Synkayvite was given, and to demonstrate the wide margin of therapeutic safety this preparation possesses. In each instance the prothrombin content of the plasma was determined before therapy was instituted, and again after 24 hours and 72 hours had elapsed. The one-stage dilution technique previously described³ was employed throughout. With this procedure a prothrombin level of 100% is considered normal.

Method. Forty-eight patients with prothrombin deficiency were studied, 31 of whom had a lowered prothrombin level due to inadequate absorption of vitamin K from the intestinal tract. The remaining 17 patients exhibited various conditions with a lowered prothrombin level of intrahepatic origin. Synkayvite was given orally to 29 patients, intramuscularly to 14 and intravenously to 5. In each case the daily dose and the initial and post-administrative prothrombin levels are given in the accompanying table (Table 1). Cases 14, 32 and 40 were more than usually interesting and are presented below in some detail.

Case Reports. CASE 14. Female, aged 35, was hospitalized with a diagnosis of postoperative common duct stricture. Jaundice of an obstructive origin had been present for 5 weeks. Bleeding from the gums and vagina had been noted for 10 days before admission.

When first determined the plasma prothrombin level was reported as 18%. Twenty mg. of Synkayvite were given intravenously each day and despite deep jaundice all evidence of hemorrhage disappeared within 4 hours of administration. Twenty-four hours after the Synkayvite was given the prothrombin level was 100%.

CASE 32. Male, aged 24, hospitalized for symptoms attributed to Banti's syndrome. On admission the plasma prothrombin level was reported as normal but fell to 75% after one month. At this time a daily dose of Synkayvite, 5 mg. by mouth was started. Within 24 hours the prothrombin level rose to 82% and at the end of 72 hours was 94%. In this case the response was most marked of all the patients suffering primarily from liver disease. It is likely that in this instance the involvement of the

liver was not so extensive as to preclude at least a partial response to the Synkayvite given.

CASE 40. Female, aged 23, admitted to the hospital with a diagnosis of acute myelogenous leukemia. An initial plasma prothrombin level of 58% was reported. Ten mg. of Synkayvite were given intramuscularly each day resulting in a rise to 60% of normal after 24 and 72 hours. However the patient expired 3 days after the last prothrombin determination had been made and it is probable that the failure of Synkayvite in this case was occasioned by the severe liver damage demonstrated at autopsy.

TABLE 1.—PROTHROMBIN BEFORE AND AFTER SYNKAYVITE

Case No.	Diagnosis	Prothrombin, % of normal			Daily dosage of tetrasodium 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester (Synkayvite), mg.
		Initial	24 hours after treatment	72 hours after treatment	
1	Carc. of head of pancreas	43	100	100	5 orally
2	Common duct stone	85	100	100	5 "
3	Common duct stone	45	100	100	5 "
4	Carc. of head of pancreas	65	100	100	5 "
5	Carc. of head of pancreas	55	100	100	10 "
6	Carc. of stomach, no jaundice	82	100	100	10 intravenously
7	Carc. of common duct	58	100	100	10 orally
8	Common duct stone	55	100	100	10 intravenously
9	Ulcer. colitis, no jaundice	28	100	100	10 "
10	Carc. of stomach, no jaundice	55	100	100	10 "
11	Common duct stone	65	100	100	10 orally
12	Carc. of head of pancreas	48	100	100	10 "
13	Carc. of head of pancreas	62	100	100	5 "
14	Common duct stricture	18	100	100	20 intravenously
15	Compl. ext. biliary fistula	65	100	100	10 orally
16	Carc. of ampulla of Vater	83	100	100	5 "
17	Common duct stone	72	100	100	10 "
18	Common duct stricture	45	100	100	15 "
19	Carc. of head of pancreas	71	100	100	10 "
20	Carc. of esophagus, no jaundice	74	100	100	10 intramuscularly
21	Carc. of stomach, no jaundice	64	100	100	10 "
22	Ulcerative colitis	43	100	100	10 "
23	Common duct stone	58	100	100	10 orally
24	Common duct stone	86	100	100	5 "
25	Carc. of common duct	57	100	100	10 "
26	Common duct stone	39	100	100	15 "
27	Compl. ext. bile fistula	55	100	100	10 "
28	Carc. of ampulla of Vater	54	100	100	10 "
29	Common duct stone	45	100	100	10 "
30	Common duct stone	85	100	100	10 "
31	Carc. of common duct	65	100	100	10 "
32	Banti's syndrome, no jaundice	75	82	94	5 "
33	Cirrhosis, jaundice	60	68	85	5 "
34	Cirrhosis, jaundice	64	65	68	5 or 10 "
35	Multiple myeloma, large liver, no jaundice	63	63	62	10 "
36	Cirrhosis, no jaundice	75	80	83	10 "
37	Cirrhosis, jaundice	75	88	85	10 "
38	Cirrhosis, jaundice	70	70	70	10 intramuscularly
39	Cirrhosis	62	66	71	10 "
40	Leukemia, large liver	58	60	60	10 "
41	Leukemia, large liver	40	43	Expired	10 "
42	Cirrhosis, jaundice	71	70	70	10 "
43	Cirrhosis, no jaundice	80	80	83	10 "
44	Metastatic carcinoma of liver, jaundice	80	80	80	10 "
45	Cirrhosis, no jaundice	75	78	85	10 "
46	Acute catarrhal jaundice	63	68	79	10 "
47	Acute catarrhal jaundice	70	73	79	10 "
48	Abscess of liver	54	55	60	10 "

Therapeutic Safety. In order to determine the low toxicity of Synkayvite, 2 essentially normal individuals were chosen as experimental subjects. Both were adult males, aged 23 and 40 years respectively, and had been hospitalized for the repair of inguinal herniæ. Pre-experimental plasma prothrombin levels were normal and each subject was then given 200 mg. of Synkayvite intraven-

ously followed by the determination of daily prothrombin levels over a 7-day period. In no instance was there noted any untoward symptoms, alteration in prothrombin level, change in hematologic picture or urine. The results are summarized in Table 2.

TABLE 2.—BLOOD VALUES IN 2 NORMAL INDIVIDUALS

	Case 1		Case 2	
	Initial	At end of 7 days	Initial	At end of 7 days
R.B.C. (in millions)	4 8	5 1	5 1	5 2
Hb. (in grams)	16	16	16	15 5
W.B.C. (in thousands) . . .	6 0	7 2	7 8	9 7
Prothrombin (%)	100	100	100	100

The blood smears were entirely normal, including differential count and character of leukocytes.

Comment. From Table 1 it will be noted that every patient (Cases 1 through 31) whose prothrombin deficiency was the result of a defective absorption of vitamin K responded rapidly; the prothrombin always returned to normal within 24 hours. The remaining 17 cases, whose prothrombin levels were not so dramatically changed, were without exception instances of intrinsic liver damage in which it is presumed the hepatic lesions were so extensive that the organ could not accelerate prothrombin production even though given an excess of the vitamin.

The vitamin K preparation employed gave satisfactory results in the patients who were subjected to major operative procedures, regardless of the route chosen for its administration. However, in general, it was noted that a more sustained effect was obtained when the oral or intramuscular route was chosen than when intravenous administration was instituted. In the latter case it seems not improbable that a greater amount of the active substance was excreted through the kidneys before its total effect could be obtained.

Recently, Allen and Julian² have emphasized the diagnostic importance of the effect of a trial dose of vitamin K in patients with jaundice and prothrombin deficiency. Patients whose hypoprothrombinemia results from inadequate absorption of the vitamin display a rapid return of prothrombin to normal within 8 to 24 hours. In those cases in which the prothrombin reduction results from primary liver disease little or no benefit from the use of the naphthoquinone is obtained. These two distinctly different responses to a trial dose of the vitamin serve as an excellent means for differentiating between intra- and extrahepatic jaundice. In applying this differential method a single dose of the vitamin is administered and the prothrombin again observed after 12 hours. In order to assure prompt response the naphthoquinone should be administered intravenously. For this purpose we have found the water soluble tetrasodium salt of 2-methyl-1, 4-naphthahydroquinone diphosphoric acid ester more advantageous than the fat soluble compounds which can only be used orally or intramuscularly in oil.

Toxic manifestations due to the administration of vitamin K or one of its preparations are apparently rare in animals or in man. Recently Molitor and Robinson¹⁴ found that in mice the oral lethal dose was approximately 200 mg. per kg. of body weight for phthiocol and 500 mg. per kg. for 2-methyl-1, 4-naphthoquinone. However, no lethal effects were observed in doses up to 25 gm. per kg. in the case of natural vitamin K (2-methyl-3-phytyl-1, 4-naphthoquinone). Foster,¹⁰ using Synkayvite, found that large doses must be given before a lethal effect is noted (450 mg. per kg. in the case of mice in which the drug was given intravenously or subcutaneously). Toxicity was observed in rabbits when 50 to 200 mg. per kg. were given. Such symptoms included an acceleration in the respiratory rate, rise in temperature, pin-point pupils and a state of anxiety and apprehension. Shimkin¹⁶ states that transitory mild collapse and respiratory embarrassment appeared early, that later the legs extended, the animal became cyanotic, the urine brown in color, and that death was the result of respiratory failure.

Experiments conducted by Foster, Smith and Ivy¹² in which large doses of Synkayvite were given over an extended period of time showed that a slight loss in weight was noted in rats fed 10 doses of 100 mg. per kg. over a 14 day period. Rabbits receiving similar doses over a 20 day period displayed a mild anemia while larger doses produced a marked aplastic anemia with a 50% mortality. These investigators also noted a yellowish-brown or pinkish-orange discoloration of the fur of rats and rabbits subjected to repeated high dosage of this drug. However no local irritation was found.

Allen¹ has reported on the daily administration of 8 mg. of menadione (2-methyl-1, 4-naphthoquinone) to a human patient over a period of 18 months. No toxic or untoward effects have been noted. This patient has continued receiving the same daily dose now for 30 months, still without any signs of toxicity. It would seem therefore that the toxic dose of the naphthoquinones apparently so greatly exceeds the therapeutic dose that there is little risk of any toxic reactions when the drug is administered in the routine treatment of the patient.

The results obtained in the present experiments indicate that the acutely toxic dose of Synkayvite seemingly is far greater than the advised therapeutic one.

Summary. 1. The tetrasodium salt of 2-methyl-1, 4-naphthoquinone diphosphoric acid ester, a water soluble vitamin K-like substance, was administered to 31 patients with obstructive jaundice and 17 with intrahepatic jaundice. This drug uniformly elevated the prothrombin in the obstructive jaundiced patients. In those patients with intrahepatic jaundice the prothrombin response was comparatively slight.

2. No toxic symptoms were noted during the course of clinical

trial with this substance, even though a single dose of as much as 200 mg. was administered in two instances. The coagulation time was not abnormally shortened.

3. This new water soluble naphthohydroquinone is especially valuable in the postoperative care of the jaundiced patient. Such patients frequently display a reduction of prothrombin a day or two after operation even though preoperative therapy was carried out. This postoperative hypoprothrombinemia can be prevented or corrected by the parenteral administration of a water soluble preparation.

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THE WATER AND ELECTROLYTE DISTRIBUTION IN DIABETES MELLITUS*

DEHYDRATION IN DIABETES

BY F. WILLIAM SUNDERMAN, M.D., PH.D.

ASSISTANT PROFESSOR OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA;
CHIEF OF DIABETIC CLINIC A, PENNSYLVANIA HOSPITAL, PHILADELPHIA, PA.

OUR present knowledge of the pathologic physiology of diabetes is due largely to the application of chemical methods to the problems presented by the patient. At the beginning of this century internal medicine had developed to a point where chemical help was indispensable in the diagnosis and treatment of the patient—especially the diabetic patient. Out of this need was developed the present clinical chemistry division of the hospital laboratory.

* Read before the Cincinnati Academy of Medicine on "Diabetic Day," March 3, 1942.

Initially, this branch of chemistry utilized the older, cumbersome methods of quantitative chemical analysis, but it soon became necessary to develop new procedures. Thus, it is questionable whether the use of insulin, or perhaps even its discovery, could have been possible without the timely improvements in the methods of analysis for blood sugar. The best methods of analyzing for sugar 50 years ago required from 100 to 500 ml. of blood and time-consuming analytical work. The development of micro-methods for blood sugar analysis, first by Bang in 1913,² however, made it possible to make analyses upon 1 ml. or less of blood within a half hour. Thus, one might ask what might be the present status of our knowledge of diabetes were it not for this great advance in methodology. In a real sense, the application of chemical methods has been the cement which has bound together the foundations of our knowledge of diabetes.

In no disease has the composition and character of the body fluids and tissues been more intensively studied than in diabetes mellitus. This applies especially to its most serious complication—diabetic acidosis. Important advances have been made in recent years in our knowledge of the distribution of the salts of the body under various normal and pathologic conditions. Gradually insight has been gained into the disturbances produced by alterations in the distribution of salts. We wish to direct attention particularly to these disturbances in diabetes mellitus. In this field of metabolic research we are especially indebted to the contributions of Gamble and his associates^{5,6} on dehydration and the mass movement of salt and water in the body; to the serum electrolyte studies of Peters,⁸ Peters and Van Slyke,⁹ of Guest and Rapoport⁷ and of others; and to the electrolyte balance studies in diabetic acidosis by Atchley, Loeb and their co-workers.¹

Our approach to the distribution of water and electrolytes in diabetes mellitus has consisted in the main of 3 types of study: (1) changes produced by the administration of glucose to diabetic patients without ketosis;¹³ (2) changes produced by the injection of insulin to severe diabetic patients;¹⁰ (3) changes observed in depancreatized dogs permitted to lapse into diabetic ketosis.¹²

The first study was designed to determine in the diabetic patient to whom glucose was administered the changes in activity of glucose and chloride in the serum as well as changes in the total content of these components.

The experimental procedure was essentially as follows: Blood serum was obtained after an overnight fast from severe diabetic patients to whom the administration of insulin was temporarily stopped. Seventy-five grams of glucose were administered to each patient and after an interval of 90 minutes, serum was again obtained.

In these studies special conditions existed such that without

direct measurement of serum volume one may draw reasonably reliable inference as to changes in the total amount of the serum components in the body. Assuming that the solids of the serum (which are between 90 and 95% protein) remain constant during the 90-minute period of the experiment (and for our purposes this assumption is acceptable), then the concentrations of the components may be expressed in relation to the solids and the percentage change in the total amount of these components may be calculated. In Table 1 are given data taken from a typical case.

TABLE 1.—EFFECT OF INGESTION OF GLUCOSE (CASE 6)

Serum	Before glucose	After glucose	Difference
Specific gravity	1 0291	1 0289	
Solids, gm./kg. serum	93 95	87 10	-6 85
Cl, mEq./liter serum	100 1	98 2	-1 9
mEq./kg. serum water	107 4	104 5	-2 9
mEq./kg. serum solids excl. glucose and Cl	1121 2	1221 1	+99 9
Glucose, mM./liter serum	8 5	19 4	+10 9
mM./kg. serum water	9 1	20 7	+11 6
mM./kg. serum solids excl. glucose and Cl	94 7	264 8	+170 1
Water, gm./liter serum	932 4	939 3	+6 9
gm./kg. serum solids excl. glucose and Cl	10441 0	11686 0	+1245 0

The concentrations of glucose and chloride before and after the administration of glucose have been expressed in relation to the water and solid concentration in the serum. It will be observed that there was an increase in the total amount of glucose (mM./kilo serum solids) as well as an increase in its concentration in the serum (mM./liter serum). Although the concentration of chloride decreased, the total amount of chloride in the serum increased. The total amount of water in the serum increased following the ingestion of glucose.

From such analyses it has been possible to calculate the percentile increase in the water of the serum and also the molal concentration of the added glucose and added chloride calculated as if it were in this added water. The percentile increases in the water of the serum after the ingestion of glucose, are shown in the upper portion of Chart 1. Our analyses require that the solution transferred to the serum with the glucose contain from 0 to 103 mEq. of chloride per kilogram of water. The addition of glucose to this saline solution usually gave a solution for which the calculated molal concentration was higher than for the fasting serum. This calculation was corroborated by an observed slight increase in the freezing-point depression in the serum obtained after glucose ingestion. In the upper portion of Chart 1 are given also the results obtained following the ingestion of glucose in 2 normal individuals. In these 2 individuals there was an outflow of water as well as of glucose and chloride. The changes in the controls are the reverse of those observed in the diabetic patients.

In Chart 2 is plotted the increase in the milliosmolar concentration of glucose in the serum against the decrease in the milliosmolar concentration of chloride. The statistically calculated regression line is: $-\Delta\pi_{Cl} = 0.369\Delta\pi_{\text{glucose}} + 1.50$. If the milliosmolar decrease in the concentration of chloride were equal to the millios-

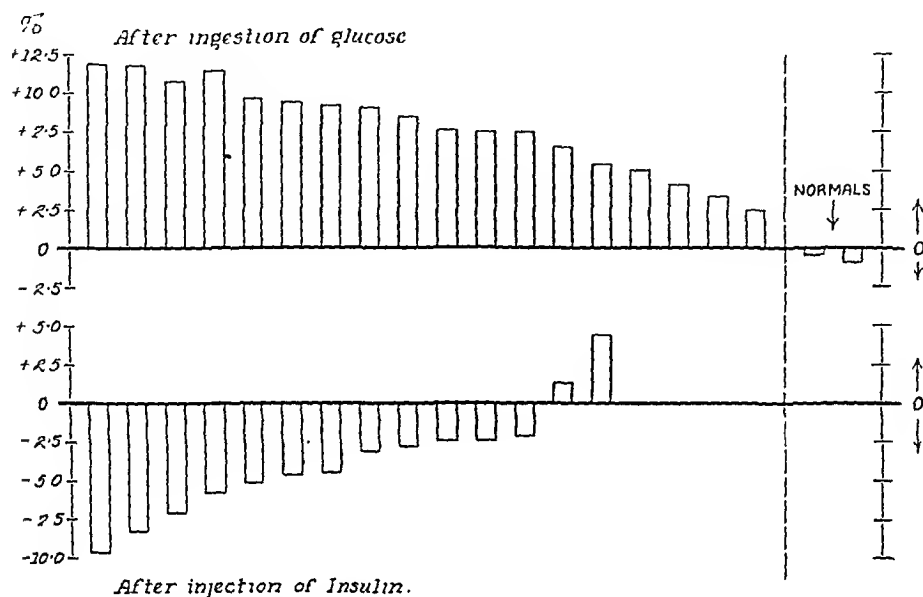


CHART 1.—Percentile change of water content in serum of diabetic patients.

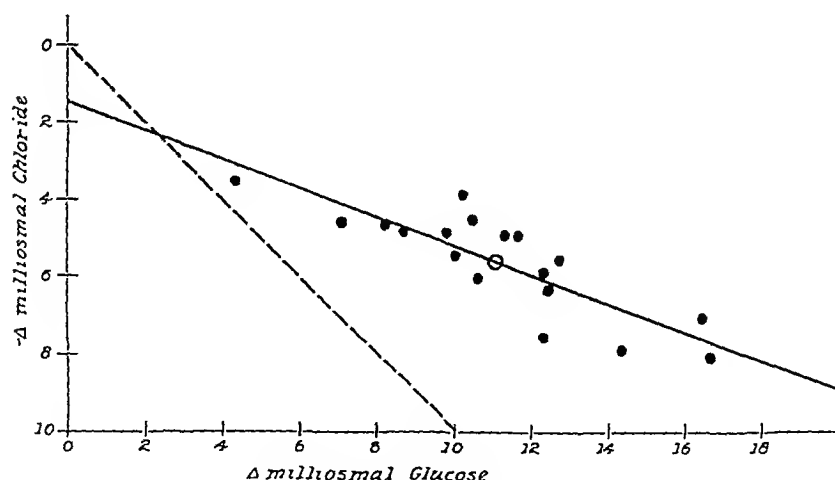


CHART 2.—Increase in osmolal concentration of glucose against decrease in osmolal concentration of chloride.

molal increase in glucose, the data would follow the dotted line. Increase in the concentration of glucose is thus not entirely compensated for osmotically by decrease in the concentration of chloride.

The simplest schematic interpretation of the situation here portrayed is that the uptake of glucose in the serum of diabetic patients

(but not in normal individuals) tends to draw water into the serum from the tissues. The water added to the serum with the glucose tends to dilute the serum electrolytes, and to set up a potential gradient for electrolyte from tissue to serum, hence an inflow of chloride into the serum. Thus in the diabetic patient a potential gradient induced with respect to glucose, induces secondarily a potential gradient with respect to electrolyte. The diuresis that usually ensues following the ingestion of glucose in diabetic patients may be a reflection of the increased content of water poured into the serum.

A second approach to the problem of the distribution of electrolytes in diabetic patients was made by determining the changes induced in the serum following the administration of large doses of insulin to diabetic patients with high blood sugars.

After a period without insulin long enough to induce marked elevation of blood sugar and after an overnight fast, sufficient blood was withdrawn for a complete analysis of the electrolytes. The patients were then given a large dose of insulin (50 to 120 units), still fasting. Following the insulin the patients were permitted to ingest water as desired. When the blood sugar had fallen to within normal limits (within 40 minutes to 3 hours), or upon the appearance of any symptoms of an insulin reaction, a second specimen of blood was removed and the study was discontinued.

In Table 2 are given data from a typical case. After insulin administration to the diabetic patients, the solids of the serum tended toward increased concentration. Assuming that the solids exclusive of glucose and chloride in the serum remain constant during the brief period of these observations, then the change in the total amounts of components in the circulating serum may be calculated. When such estimations are made, there can be demonstrated a decrease in the total amounts of glucose, chloride, and water in the serum.

TABLE 2.—EFFECT OF INSULIN (CASE 6)

Serum	Before insulin	After insulin	Difference
Specific gravity	1 0289	1 0292	
Solids, gm./kg. serum	88 70	93 50	+4 80
Cl, mEq./liter serum	96 1	99 4	+3 3
mEq./kg. serum water	102 5	106 5	+4 0
mEq./kg. serum solids excl. glucose and Cl	1174 8	1109 1	-65 7
Glucose, mM./liter serum	21 4	4 8	-16 6
mM./kg. serum water	22 8	5 2	-17 6
mM./kg. serum solids excl. glucose and Cl	261 6	53 9	-207 7
Water, gm./liter serum	937 6	933 0	-4 6
gm./kg. serum solids excl. glucose and Cl	11463 0	10420 0	-1043 0

In the lower portion of Chart 1 are shown the percentile decreases in the water of the serum after injection of insulin. This anhydremia which develops when insulin is given has long been recognized.

Following the administration of insulin to dogs, Drabkin, Page and Edwards,³ and Drabkin⁴ demonstrated that there was increased concentration of hemoglobin, increased erythrocyte counts and reduction in the plasma volume.

After the administration of insulin, the concentration of serum sugar was decreased in the serum in all of the diabetic patients. It is interesting to note, however, that in 4 of the observations the study had to be terminated at a time when the concentration of serum sugar was above 200 mg. per 100 ml. because of the appearance of insulin reactions. In these patients the shocklike reactions occurred when there had been a high initial blood sugar with fall in concentration of sugar amounting to 1 mg. or more per 100 ml. per minute. Neither high initial serum sugar nor rapid rate of fall independently induced reactions but the combination of these two factors did so. These shocklike reactions, which we could not distinguish clinically from the ordinary insulin reaction, developed while the serum sugar concentrations were still above 200 mg. per 100 ml. They were promptly relieved by the administration of glucose.

Before insulin administration the chloride concentration in the serum of the diabetic patients decreased below the normal range in 13 out of 17 observations. After insulin administration in each case the chloride concentration was increased above the original value, the increase after insulin amounting to as much as 7.6 mEq. per liter of serum. Similar relationships were observed with respect to the total base and sodium concentrations in serum (as with chloride). In the majority of cases the concentration of sodium and of total base were increased above the original values. As with the chloride measurements, it can be demonstrated that, although the concentration of these components was increased after insulin, nevertheless, the total amounts of total base and sodium in the circulating serum were decreased. The changes in the serum of diabetic patients following the injection of insulin were essentially the reverse of those observed when these patients received glucose without insulin.

The direction in which changes occurred in the distribution of glucose and chloride in the serum of severe diabetic patients without ketosis has been summarized in Table 3.

TABLE 3.—CHANGES OBSERVED IN THE SERUM OF DIABETIC PATIENTS

Serum	Concentration	Total amount
<i>After Ingestion of Glucose</i>		
Glucose	>	>
Chloride, total base (volume >)	<	>
<i>After Injection of Insulin</i>		
Glucose	<	<
Chloride, total base (volume <)	>	<

The third approach to the problem of the distribution of water and electrolytes was designed to determine, by direct methods, the changes in the concentration and in the total amount of components in the circulating serum during the ketosis of experimental diabetes induced in dogs by pancreatectomy. In addition to measuring the serum volume directly by means of dye injection, the amount of extracellular fluid was estimated by the NaCNS method.

Large healthy dogs were kept under constant conditions in their cages for a week or more before studies were made. After this preliminary period and a fasting period of 24 hours, the animals were given nembutal parenterally, following which measurement of serum volume was made by the vital red method¹¹ and blood was withdrawn for chemical analyses. Total pancreatectomy was then performed. After operation, the animals were given maintenance doses of insulin until recovery had occurred. After the operative scars had completely healed and the animals were regarded as in acceptably good condition, insulin therapy was completely withheld and the animals were permitted to go into ketosis. Final measurements were made when ketosis was well developed. The period of time required for the development of severe ketosis varied with individual dogs, some remaining active for as long as 3 weeks following the withdrawal of insulin. All of the animals had heavy ketonuria for several days before the final measurements were made, although some had relatively little fall in concentration of serum CO_2 .

Since all of the depancreatized dogs lost greatly in body weight, the effect of ketosis following simple fasting was also studied in measurements on 2 dogs before and after losing a fourth of their body weight.

Since the changes in the individual serum constituents were all consistent in the depancreatized dogs we present only the average of the serum values obtained during the control period and during ketosis. The results of these analyses are given in Table 4.

TABLE 4.—AVERAGE OF SERUM ANALYSES (6 DIABETIC DOGS)

	Period	
	Control	Diabetic keto-is
Serum volume, ml./kg. body weight	52.8	70.3
Sugar, mg./100 ml.	106.0	450.0
Solids, gm./100	7.4	6.7
Protein, ml. gm./100	5.4	5.0
F.A., mM./L.	9.3	17.0
Cholesterol, mg./100 ml.	182.0	184.0
Total base, mEq./L.	147.8	139.8
Chloride CO_2 :		
mEq./L.	109.4	101.5
Volume %	57.0	37.0
Undetermined anion, mEq./L.	3.8	13.4
Δ , °C.	-0.545	-0.593
Urea N, mg./100 ml.	22.0	30.0

During the control period the average serum volume was 52.8 ml. per kilo of body weight; all of these measurements were within the normal range of values previously obtained on normal dogs in our laboratory. Following ketosis the serum volume per kilo of body weight increased in all of the dogs (averaging 70.3 ml. per kilo).

The concentration of sugar increased from the average value of 106 mg. per 100 ml. during the control period to 450 ml. during ketosis. The concentrations of serum solids and serum proteins decreased during ketosis. The concentration of fatty acids increased to approximately twice the normal value. Cholesterol estimations were made in 5 animals; 2 exhibited increased cholesterol concentrations during ketosis; 2, decreased concentrations; and 1 exhibited no change.

The concentrations of total base, Cl, and CO_2 decreased in the sera of all of the depancreatized dogs during ketosis. The concentration of undetermined anions was obtained by adding the values of BCl, BHCO_3 and BPr and subtracting this sum from the value for total base. In all but one of the dogs the concentrations of undetermined anions increased greatly during ketosis.

The freezing-point depression of the sera increased above the value obtained initially. The decrease in the osmolar concentrations of total base during ketosis was thus more than compensated by the increased osmolar concentration of sugar and other non-electrolytes. The concentration of urea increased during ketosis.

As all of the diabetic dogs suffered severe reductions in body weight, comparison of similar measurements was made in dogs subjected to simple fasting. The result of these measurements is not given in the table. However, with the exception of a slight reduction in the concentration of serum protein and cholesterol and a slight increase in the concentration of undetermined anion, the concentrations of serum components exhibited no essential change during fasting.

The amounts of components in the circulating serum were calculated during the control period and during ketosis and were compared in two ways. First, the total amount of a given component in the serum during ketosis was compared to the total amount of that component present during the control measurements. Second, the total amount of a given component *per kilo of body weight* during ketosis was compared to the total amount of that component per kilo of body weight during the control measurements. In Table 5 are given the average of the percentile changes in the amounts of serum components during ketosis as related (1) to the total amount present in the circulation during the control period, and (2) as related to the amount present per kilo of body weight during the control period. The values in the depancreatized animals are compared to those obtained in the fasted animal.

From the time of the initial to the final measurements the diabetic

dogs lost weight amounting from 25 to 43% (average, 33%). Final measurements were made in the fasted animals after a reduction of 26% of the body weight.

In Table 5 it will be seen that although the total amount of serum present in the circulation during ketosis was 10% less than in the healthy state, the serum volume per kilo of body weight was on the average, 29% greater than in the healthy state. In the fasted animals the total serum volume decreased in proportion to the reduction in body weight (24%) so that the serum volume per kilo of body weight remained constant.

TABLE 5.—PERCENTILE CHANGE IN SERUM CONTENTS DURING KETOSIS

	Diabetes		Fasting	
	Total	Per unit of body weight — 33	Total	Per unit of body weight — 26
Body weight				
Serum:				
Volume	-10	+29	-24	+2
Water	-0 8	+33	-24	+3
Total base	-15	+23	-26	0
Cl	-16	+25	-27	-2
BPr	-16	+20	-30	-7
BHCO ₂	-45	-17	-36	0
Sugar	+282	+431	-31	-7
Cholesterol	+6	+49	-37	-16

In the diabetic dogs the total amount of water in the serum during ketosis was unchanged although the serum water per unit of body weight increased 33%. In the starved dog the total serum decreased in proportion to the decrease in body weight, so that the serum water per unit of body weight was unchanged. The total amounts of total base, Cl, and BPr in the diabetic dogs all decreased during ketosis, although the amounts of all of these components per unit of body weight increased. In the fasted animal the amounts of these components per kilo of body weight remained almost unchanged during ketosis.

Of all the serum components studied in the diabetic dog and expressed per unit of body weight, only the *bicarbonate content* per kilo of body weight was consistently decreased. These analyses of serum in the depancreatized animals are in marked contrast to those obtained during the ketosis of fasting. In the fasted animal the total amount of each of the serum components per unit of body weight as well as the serum volume per unit of body weight remained practically unchanged with the exception of protein and cholesterol which were decreased.

The results of the measurements of the extracellular water in two of the depancreatized dogs (E₂ and E₃) and of one fasted dog (E₆) are shown in Table 6. During ketosis in the depancreatized dogs, extracellular water per unit of body weight increased 12.5 and 8.4% respectively, while in the fasted animal the extracellular

water increased only 3.7%, which may be within our experimental error. In the diabetic animals the total amount of extracellular water present during ketosis was little if at all changed from that measured during the normal state in spite of loss of body weight.

TABLE 6.—EXTRACELLULAR WATER

Dog	Period	Body weight, kg.	Extracellular water	
			Kg.	% of body weight
E ₂	Control	15.3	4.89	31.0
	Diabetic ketosis	11.3	4.89	43.5
E ₅	Control	33.8	10.64	31.5
	Diabetic ketosis	25.5	10.16	39.9
E ₆	Control	16.2	5.44	33.6
	Fasting	12.1	4.51	37.3

During the development of diabetic acidosis excessive amounts of water and electrolytes are excreted in the urine. Atchley, Loeb and their associates,¹ in balance studies of patients during the early stages of diabetic acidosis produced by the withdrawal of insulin, observed excretion of base greatly in excess of the amounts ingested. Most striking, perhaps, in their observations was the increased urinary excretion of intracellular constituents (K, PO₄, SO₄ and N) during the acidosis periods. In one of their patients the loss of potassium exceeded the loss of sodium. A question that obviously arises is: which space or spaces in the body supply the water and electrolytes that are excreted?

It is the usually accepted concept that dehydration is accompanied by a withdrawal of water from both the extra- and intracellular fluid compartments and that the serum volume falls when the interstitial fluids attain a certain minimal value. Support for this theory has been derived chiefly from Na and K losses from the body. However, our studies would indicate that during the dehydration of diabetic ketosis the water and electrolytes apparently do not come from the circulating serum, since the total amounts of these components may be increased. It would seem to us that, in the main, the extracellular fluid provides the Na and Cl for excretion; the cells supply the K, PO₄, SO₄, and N, and the intracellular space provides the water.

Chart 3 is our schematic representation of the electrolyte changes in the body during the course of diabetic acidosis. The first column represents the normal concentration of the electrolytes of the serum, the normal volume of serum and the normal amount of water and electrolyte in the extravascular spaces. During the development of diabetic acidosis, ketone acids (β -hydroxybutyric and diacetic acids) increase in excessive amounts. The increase in these acids displaces HCO₃⁻ which is expired into the air as CO₂. The kidneys tend to maintain a normal electrolyte pattern by excreting organic acids in the urine as free acids and in combination with NH₃⁺. In this process the production of NH₃⁺ is insufficient for combina-

tion with the organic acids awaiting excretion and as a consequence, fixed base is excreted for the purpose. This loss of base necessitates the withdrawal of water if isotonicity of the body fluids is to be maintained. Coincident with the withdrawal of base and water from the tissues, the serum volume and the total amounts of base and chloride in the serum increase. Increasing concentrations of glucose, urea and other non-electrolytes appearing in the serum

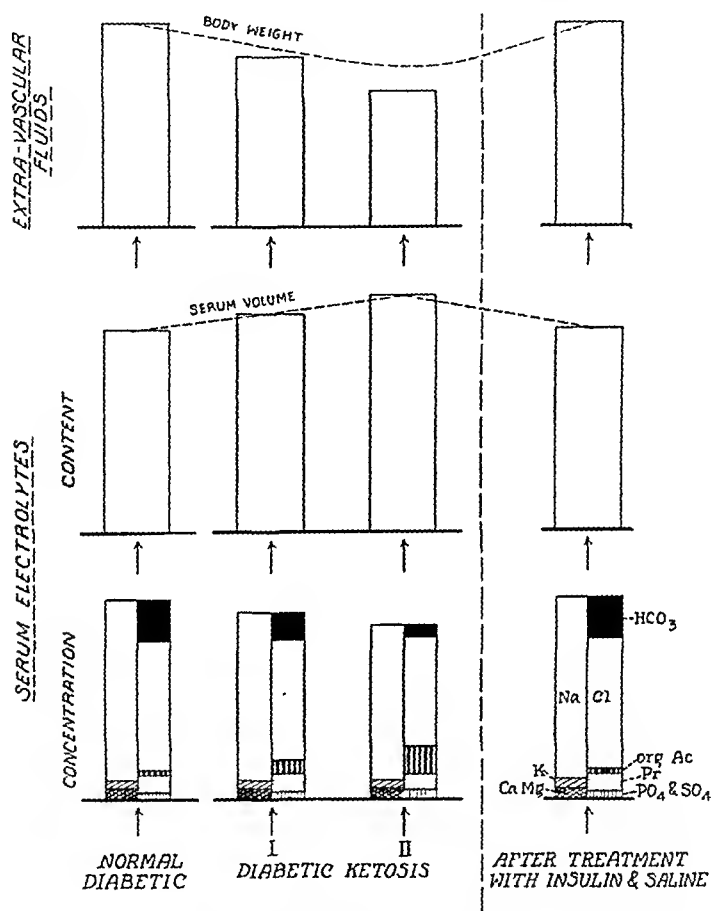


CHART 3.—Schemata demonstrating changes in relation to diabetic ketosis.

elevate the total osmotic pressure of the serum. In partial compensation the concentration of the electrolytes may be decreased by increase of serum water, although the total amount of electrolyte is increased.

Finally, as shown in the third column, the extravascular fluids become greatly depleted and, with the continued demand for fixed base to combine with the organic acids, chloride begins to release its base by its secretion as HCl in the vomitus. The protoplasmic

structure of the organism is soon unable to withstand further strain, and unless therapy is instituted, death ensues. In the last column is shown a return to the normal distribution after administration of insulin and saline.

A most conspicuous feature in the development of diabetic acidosis leading to coma is the depletion of fixed base and water. Administration of saline solutions alone will not alleviate the resulting dehydration. However, the administration of *insulin* together with saline solutions results in transfer of water and electrolytes from the serum to the extravascular fluids and is recognized as the only successful method of combating the dehydration of diabetic ketosis. The action of insulin is followed by a decreased production of organic acids and, as a consequence, the electrolyte pattern and osmotic pressure of the serum gradually return to their normal values. Such, in outline, is the rôle played by the electrolytes during the course of diabetic coma.

The extreme dehydration occurring in diabetic ketosis is perhaps most strikingly shown by the gain in weight during convalescence. In one patient, recently studied, the gain in weight amounted to 8 pounds in 4 days.

The occurrence of coma in diabetic patients is precipitated by acute infections in more than 50% of the cases. During the early stages of such an infection the patient is often urged to drink copious quantities of water; or, because of the beginning of dehydration, he may possess a craving for water. This water, if unaccompanied by salt, cannot be stored and is excreted. In its excretion it tends to carry salt with it, thus further depleting the body's reserve of base. Therefore, the ingestion of water alone may hasten dehydration in the diabetic patient, whereas water given with the proper amount of salt is one of the simplest and most effective methods of forestalling dehydration. However, and above all, it must be emphasized that in providing for a return toward the normal distribution of water and electrolytes in the vascular and extravascular fluids of the diabetic patient with ketosis, *insulin*, in addition to saline solutions, is essential. No lasting significant beneficial effects will be secured when saline solutions are given diabetic patients in coma unless adequate amounts of insulin are also given with saline.

Summary. We have indicated the altered distributions of body water and electrolytes associated with diabetes. Administration of glucose to the severely diabetic individual without ketosis leads to a transfer into the circulating serum of water, NaCl, and glucose from the body tissues, so that the total amount of these components in the serum is increased, even though the concentrations of the electrolytes in the serum may actually be decreased. Likewise, in depancreatized dogs with ketosis there is a continued transfer of water, NaCl, and glucose from the tissues into the circulation. On the other hand, administration of insulin to the diabetic human

produces a reversal of these processes and causes transfer of water and electrolytes from the serum into the tissues. We wish to emphasize this action of insulin in readjusting the partition of water and electrolytes in diabetic individuals as important among its varied and complex effects.

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FAMILIAL CRETINISM

TWO BROTHERS EXHIBITING THYROID DEFICIENCY AND EPIPHYSEAL DYSGENESIS

BY I. P. BRONSTEIN, M.D.

ASSOCIATE PROFESSOR OF PEDIATRICS

L. E. BOWER, M.D.

ASSISTANT PROFESSOR OF PEDIATRICS

AND

J. MURPHY, M.D.

CLINICAL ASSISTANT IN PEDIATRICS
CHICAGO, ILL.

(From the Department of Pediatrics [Endocrine Clinic], University of Illinois College of Medicine and the Research and Educational and Cook County Hospitals)

FAMILIAL cretinism is a rarity in this country. It is not uncommon where thyroid deficiency is endemic, as in Switzerland. In the review of the American literature, we were able to find but very few instances, and none quite similar to the one we are reporting.

Hosen⁷ described hypothyroidism in twins. Reilly¹² reported a family with physical characteristics resembling hypothyroidism. Shelton¹⁵ described 4 cases of hypothyroidism in one family in which the stature was under the accepted standards. Stevens¹⁶ reported 4 cases which he categorized as sporadic cretinism; Goodkind and Higgins⁴ mention the occurrence in 2 siblings. Watson¹⁷ reported 3 cases in one family which he termed cretinoid amentia. Herrman⁵ presented 2 different families with 3 cases of hypothyroidism.

Sanderson¹⁴ reported 3 cases in one family which he termed sporadic cretinism. Ebricht³ and MacIlwaine¹⁰ both reported cases of myxedema in pregnant women whose children developed cretinism following birth. Johannsen⁸ reported a Scandinavian family in which he was fairly certain that 3 of the members were cretins. Familial cretinism or myxedema is discussed by Albrecht,¹ Laure and Patry,⁹ Pighini,¹¹ Artom and Fornara,² but careful study of these articles fails to reveal a similarity to our patients.

Case Reports. CASE 1. E. D., a 13-year-old male, a typical sporadic cretin, entered the Cook County Hospital in February, 1940. He was admitted because of a prolapsed rectum which was reduced under surgical anesthesia. On questioning the parents about medical attention for this child it was found that none had been sought because of the presumable failure of medication on a previous sibling for a similar condition. This boy will be described subsequently.

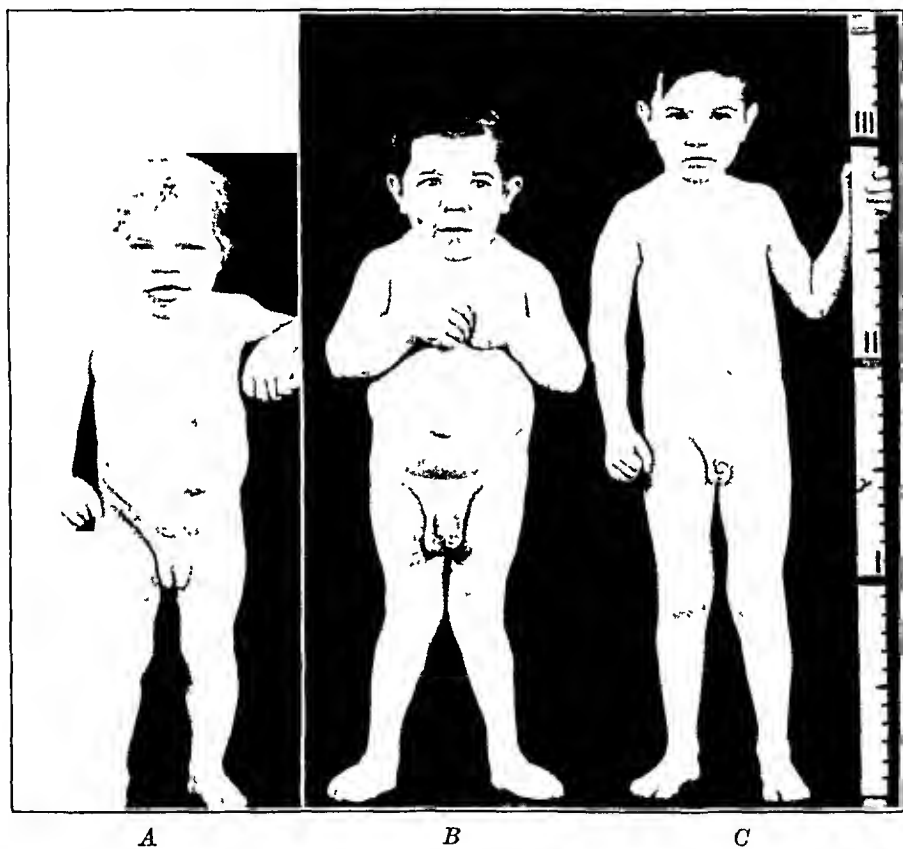


FIG. 1.—A, Cretin, aged 13 years. B, Brother, aged 23 years. C, Normal boy of 7 for comparison.

The family history is one of the interesting features of this report. Two of the mother's first cousins had thyroidectomies performed 10 years ago. The mother's sister, now a resident of German Poland, is reported to have an enlarged thyroid gland. The father and mother appear to have adequate physical and mental development. There are 7 children: the oldest, a girl of 24 years who had a thyroidectomy at the age of 21 years; 4 others who are apparently normal, and our patients.

At entrance, E. D. weighed $39\frac{1}{2}$ pounds and was $36\frac{1}{2}$ inches tall (Fig. 1A). He spoke no syllables, carried out no simple commands, was unable to walk, and had the intelligence quotient of an 18-month-old infant. The dwarfed stature and mental inadequacy, in addition to supraclavicular fat pads, macroglossia, large abdomen and dry skin readily identified him.

Roentgenograms of the bones revealed marked retardation of skeletal growth, with fragmentation and stippling of the epiphyses of the humeri and femori. The ossification of the wrist showed 3 carpal centers. Marked caries and in some instances only fragments of teeth were present. The electrocardiogram revealed low voltage in all leads.

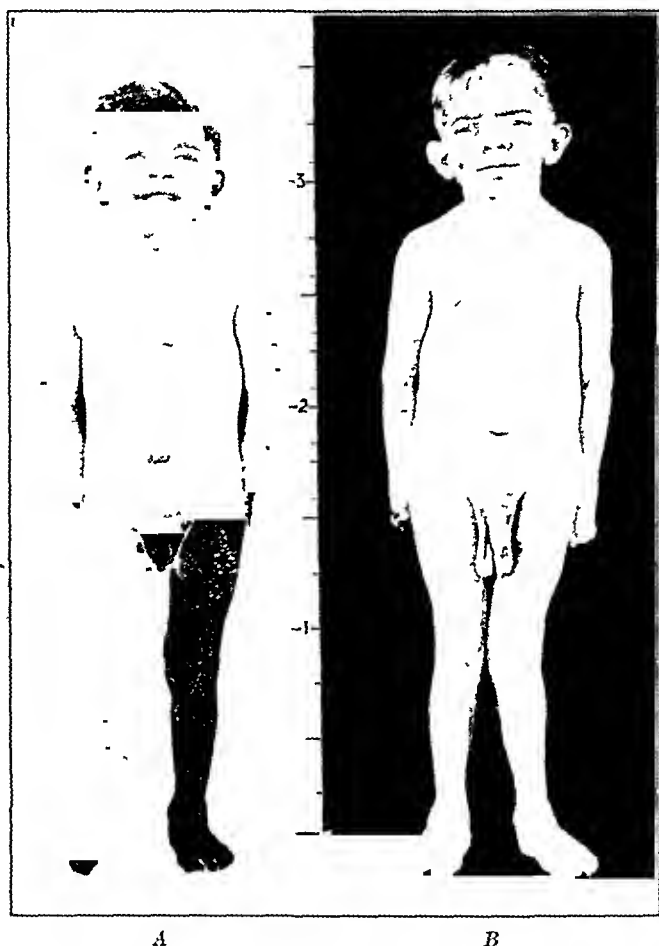


FIG. 2.—A, Case 1, 17 months later. B, Case 2, 16 months later.

A biopsy obtained from a supraclavicular fat pad revealed a fibrolipomatous structure. The blood Kahn and the Mantoux, intracutaneous 1:1000 tests were negative. Vascular microscopy and tonoscopy (performed by Dr. Olkon) revealed capillary deficit and stasis, vasomotor instability and atherosclerotic-like manifestations. These changes were interpreted as suggestive of metabolic disharmony, nutritional deficit, and early senility. The patient did not cooperate sufficiently to determine the basal metabolic rate.

The boy was seen 17 months later (Fig. 2A). His activity had improved, he talked more, walked, and carried out simple commands. He received 2 grains of thyroid a day without ill effects.

CASE 2. F. D., a 22-year-old white male, brother of the former, a typical sporadic cretin, entered the Research Hospital in March 1940. He was a full-term infant, second born of a normal 9-month pregnancy with a 1-hour labor. When the boy reached the age of 3 years he was hospitalized because he did not grow and develop like the first child. His skin was dry, tongue large, as were also the head and abdomen. He remained in the hospital for 1 year, at the end of which time he sat, walked and ate by himself, all of which he could not do before. From the age of 4 until the present time the boy's condition was neglected.

Upon entrance, F. D. weighed 46 pounds and was 38½ inches tall, and was readily recognized as a typical cretin (Fig. 1B). He spoke only in monosyllables, carried out a few simple commands, and had an intelligence quotient of a 3-year-old.

In a recent report by one of us,⁶ this patient was adequately described and therefore we will dispense with the details of the history, physical examination and laboratory findings.

The patient was last seen (Fig. 2B) at the same time as his brother. He weighed 47 pounds and was 43 inches tall. He was no longer constipated, obeyed commands, was more congenial, and his color had likewise improved. This patient received 2 grains of thyroid extract daily without ill effects.

Comment and Summary. Two brothers who were readily identified as typical cretins are reported from a family that had a history of frequent thyroid trouble. This is the first time we have encountered this separation in an experience with some 60 thyroid deficient children. Review of the American literature indicates the rarity of this condition.

These brothers, in addition, exhibited epiphyseal dysgenesis which has been adequately reported in the recent literature^{13,18} and therefore needs no comment on our part.

We wish to emphasize the degree of improvement made in both boys, but especially in the 23-year-old one, who tolerates his thyroid medication well.

In addition we were able to obtain a biopsy of the supraclavicular fat pad, and perform vascular and tonoscopic studies.

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POST-OPERATIVE ACHYLIA PANCREATICA: FAT AND
PROTEIN ABSORPTION WITH AND WITHOUT
REPLACEMENT THERAPY

REPORT OF A CASE

BY MICHAEL LAKE, M.D.

INSTRUCTOR IN MEDICINE

NELSON W. CORNELL, M.D.

ASSISTANT PROFESSOR OF CLINICAL SURGERY

AND

HAROLD E. HARRISON, M.D.

ASSISTANT PROFESSOR OF PEDIATRICS

NEW YORK, N. Y.

(From the New York Hospital and the Departments of Medicine, Surgery and Pediatrics, Cornell University Medical College)

SINCE Allen Whipple⁸ demonstrated that the head of the pancreas can be successfully resected, interest has been revived concerning the importance of the pancreatic enzymes in the digestion and absorption of food. Beazell, Schmidt, and Ivy² recently reported 4 cases of achylia pancreatica as the result of chronic pancreatitis which had been studied with and without replacement therapy. They pointed out that the number of such properly diagnosed and well studied patients are few, and that the general impression that oral pancreatic enzyme therapy in man is not of value is inconsistent with the results of animal experimentation. In each of their 4 cases they demonstrated that (1) the pancreatic enzymes were absent from the duodenum, (2) an excess of both fat and nitrogen was present in the feces, (3) increased absorption of both took place when substitution therapy was instituted, so that the quantity of fat excreted in the stool was decreased by 63%, and of nitrogen by 62%. Clinically, there was a decrease in the frequency and bulk of the stools, gain in weight and increased strength. They gave a daily dose of 24 gm. of their pancreatic preparation which they estimated replaced only about 15% of the normal daily secretion.

Whipple and Bauman,⁹ on the contrary, as the result of their experience with patients in whom the head of the pancreas had been resected for carcinoma, concluded that normal fat absorption is possible when no pancreatic juice enters the intestine. They reported studies in 4 such patients in 1 of whom an autopsy revealed no pancreatic communication with the small intestine. They believed it safe to assume, because of the operative procedures, that their other patients also had no pancreatic juice in the intestine, although in 1 case they state that the gastric contents showed considerable trypsin and some lipase, which they suggest may be the result of a compensatory increase in the activity of other glands. However,

Koskowski and Ivy's⁴ work on depancreatized dogs does not support this theory.

We recently had the opportunity of studying the fat, protein, calcium and phosphorus absorption in a patient, following resection of the head of the pancreas for carcinoma. The total absence of pancreatic enzymes following operation was demonstrated by examination of the jejunal contents both before and after the intravenous injection of secretin.

Method. The technique of Ågren and Lagerlöf¹ was used to obtain, by means of a double lumen tube and constant suction, the contents of the upper jejunum uncontaminated by gastric juice. The effects of oral administration of 24 gm. a day of a potent pancreatic preparation* were determined. We then reduced the dosage to 12 gm. a day, to note the effects of a smaller dose. Shortly after this was done a biliary fistula developed and bile disappeared from the feces. The study was continued, however, in order to observe the effectiveness of replacement therapy in the absence of bile (period IV).

Case Report. E. G., a 25-year-old female with previous good health, was admitted on June 20, 1941, complaining of attacks of epigastric and right upper quadrant pain for 1 year, not related to meals and without nausea or vomiting. Following the last attack 3 weeks previously, she developed anorexia, clay-colored stools, dark urine, pruritis confined chiefly to the feet, and lost 7 pounds in weight.

Examination showed jaundice, right-sided abdominal spasm, an enlarged liver, and a hard fixed mass 3 cm. in diameter above the umbilicus.

The icteric index was 17 and rose to 30; urinalysis showed a slight trace of albumin and was strongly positive for bile; she was slightly anemic, the white count and differential were normal. The stools were at first brown, later grayish and soft and contained no blood. The blood prothrombin level rose from 41% to 85% after an intramuscular injection of vitamin K.

Laparotomy revealed considerable enlargement of the right lobe of the liver, and tremendously dilated gall bladder, cystic and common ducts. There was a large, hard, nodular growth involving the head of the pancreas and several large lymph nodes were present along the superior mesenteric vessels.

The following operations were performed in two stages: Ligation of the common duct, cholecysto-jejunostomy and jejuno-jejunostomy (end to side), with biopsy of mass. Posterior gastro-enterostomy with resection of the first and second portions of the duodenum with entire head of the pancreas, and a partial gastrectomy were done one month after the first operation.

Histologic examination of the mass removed at operation showed the presence of a medullary carcinoma of the pancreas with metastases to the regional lymph nodes.

The last operation was performed on August 11, 1941. The jaundice cleared, but she was unable to regain weight in spite of a good appetite, and passed 2 or 3 soft, bulky, foul, grayish stools daily. On October 16, 1941 there was a rise in temperature, abdominal pain, and jaundice, and a biliary fistula opened in the operative scar. This promptly subsided and the jaundice cleared until November 8, 1941, when these symptoms recurred and lasted for about 10 days, during which time bile disappeared from the stools. These episodes were thought to be due to stagnation of bile in the stump of the common duct which acted as a valve to close off the cystic duct and thus prevented passage of bile between the gall bladder and the jejunum through the operative anastomosis.

* Holadin, in 5 grain enteric capsules, was supplied by Fairchild Bros. & Foster.

Liver function tests remained normal. Glucose tolerance tests, both oral and intravenous, gave normal curves.

At the present time, one year following the second operation; the patient has begun to complain of symptoms, similar to those at the onset of the illness, which indicate the probable recurrence of the carcinoma.

Methods of Study. Studies of the fecal loss of fat, nitrogen, calcium and phosphorus were conducted in 4 periods of 3 or 5 days each. The first 2 periods were control determinations without pancreatic enzyme administration. In period III, 24 gm. of pancreatic extract (Holadin) in enteric coated capsules were given daily, 4 gm. before and 4 gm. after each meal. In period IV, 12 gm. of Holadin were given daily. On the day preceding this period the patient became jaundiced and remained so during the 5 days of collection. No bile was present in the feces. Carmine red was given at the beginning and end of each period to mark the stools which were collected quantitatively, dried and analyzed by standard methods for fat, nitrogen, calcium and phosphorus.

Results. The results of these studies are summarized in Table 1. The average daily fecal nitrogen of normal individuals on liberal diets does not exceed 2.3 gm. and the average fecal lipid is between 7 and 10 gm.² The analyses in periods I and II without enzyme therapy showed a marked loss of nitrogen and fat in the feces.

TABLE 1.—EFFECT OF PANCREATIC ENZYMES ON EXCRETION OF FAT, NITROGEN, CALCIUM AND PHOSPHORUS IN THE STOOLS

(Average Daily Excretion in Grams and as Per Cent of Intake)

Period	Treatment	Dry weight feces	Fat		N		Ca		P	
			Gm.	%	Gm.	%	Gm.	%	Gm.	%
I*	None	102	49.0	65	4.6	38				
II†	None	132	70.7	71	6.5	54	1.06	106	0.95	62
III†	24 gm. Holadin	62	28.2	28	2.3	16†	1.0	100	0.67	45
IV†	12 gm. Holadin	96	44.8	45	3.1	23†	1.14	114	0.74	50

* Diet—protein 75 gm., fat 75 gm., carbohydrate 250 gm.

† Diet—protein 75 gm., fat 100 gm., carbohydrate 300 gm., calcium 1 gm., phosphorus 1.5 gm.

‡ N of Holadin added in intake in computing percentages.

This loss in period II represents 801 calories a day. When Holadin was given this loss was greatly reduced, in the case of nitrogen by 65% and of fat by 60%, a result almost identical with that obtained by Beazell, Schmidt and Ivy (nitrogen 62%, fat 63.3%). The dried weight of the feces was decreased by 59%, and an average of 490 calories a day otherwise lost in the stool was made available. In period IV, when bile was absent from the intestine and 12 gm. of pancreatic extract were given, analysis of the feces showed a loss of 45% of the fat intake and 25% of the nitrogen, as against a fecal loss of 71% of fat and 54% of nitrogen in period II when bile was present but pancreatic enzymes were not. This indicates that in the absence of bile pancreatic lipase is still effective in promoting absorption of fat.

During period III, when pancreatic enzymes were given and bile was present, the stools were normal in appearance and the patient felt stronger and gained weight.

In a second patient with carcinoma of the head of the pancreas successfully treated by resection of the pancreas by Dr. W. D.

Andrus, steatorrhea also developed. When 12 gm. of Holadin were given to this subject daily the fecal fat loss decreased from 31 to 21 gm. and the nitrogen excretion from 3.7 to 2.7 gm. per day. The total weight and water content of the stools were also decreased.

Calcium and Phosphorus Excretion. In all of the periods the fecal excretion of calcium was approximately equal to the dietary intake so that the patient must have shown a continued negative balance of calcium during this study. The association of increased fecal loss of calcium with steatorrhea is well recognized.⁶ The lack of effect of pancreatic enzyme administration upon intestinal absorption of calcium despite the marked improvement in the absorption of fat is of interest. Even during period III, in which 24 gm. of Holadin were given daily, the fecal excretion of fat, although diminished, is still abnormally high and may account for the continued loss of calcium. A second explanation may be that a deficiency of vitamin D existed as the result of long standing steatorrhea and was not corrected during the short period in which pancreatic enzymes were given.

The fecal excretion of phosphorus was somewhat increased during the period in which no treatment was given, and was reduced to a more nearly normal value when Holadin was given.

Vitamin A Absorption. Vitamin A absorption tests were made before pancreatic enzyme treatment was started and also with treatment. The concentration of vitamin A in the plasma was determined by the method of Kimble³ in the fasting state and 3 and 5 hours after the oral administration of 300,000 units of vitamin A. The results are shown in Table 2. In normal controls a marked rise in the plasma vitamin A is found following the administration of the vitamin A concentrate. In the initial test in this patient the fasting level is within normal limits. However, there is no rise following the ingestion of the vitamin A. When pancreatic enzymes were given, the fasting level was found to be higher than in the pre-treatment period and a gradual increase in the concentration of vitamin A in the plasma was found subsequent to the administration of vitamin A. The impaired absorption of vitamin A shown by this patient is in agreement with the findings of May and McCreary⁵ in children with pancreatic fibrosis, and with those of Ralli, Pariente, Flaum and Waterhouse⁷ in depancreatized dogs.

TABLE 2.—VITAMIN A ABSORPTION IN THE UNTREATED STATE AND FOLLOWING ADMINISTRATION OF PANCREATIC ENZYMES

(Plasma Vitamin A—Micrograms per 100 cc.)

	Fasting	3 hours	5 hours
Patient—Untreated	48	44	39
Patient—Holadin, 24 gm. a day for 16 days	77	84	94
Normal females	38-62	..	189-720

300,000 units of vitamin A in a concentrated solution in oil given orally following drawing of initial blood specimen.

(These determinations were made by Dr. Walter R. Golden of the Department of Public Health and Preventive Medicine.)

Conclusions. 1. A case of successful resection of the head of the pancreas for carcinoma in a woman of 25 years is reported.

2. The total absence of pancreatic enzymes from the jejunum was demonstrated.

3. A marked loss of fat and nitrogen and an abnormally high excretion of calcium in the feces were found.

4. The fecal loss of protein and fat was markedly diminished by oral replacement therapy, but the calcium loss was not materially affected during the short period of observation. Clinical improvement and gain in weight occurred. The defective absorption of vitamin A in this patient was also improved during the period of pancreatic enzyme therapy.

5. The findings during a period of obstructive jaundice suggest that pancreatic enzymes are active in the absence of bile and are relatively more important than bile in the utilization of fat.

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A NOTE ON THE EVALUATION OF PRIVINE HCL AS A NASAL VASOCONSTRICTOR

BY NOAH D. FABRICANT, M.D.

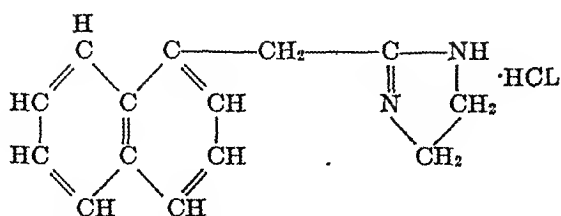
AND

O. E. VAN ALYEA, M.D.

CHICAGO, ILL.

IN the light of recent advances in nasal physiology and the attendant efforts to improve nasal medication, the introduction of Privine HCL as a nasal vasoconstrictor may prove of interest. Privine HCL* belongs to a new series of imidazoline derivatives recently synthesized and investigated for their biologic effects.³ Chemically a 2-naphthyl-methyl imidazoline, it is a crystalline, colorless substance, melting at 252°-253° C., and is readily soluble in either water or saline solution. Privine HCL has the following structural formula:

* Privine HCL was supplied by Ciba Pharmaceutical Products in the form of an aqueous, isotonic, buffered solution containing phosphates, ehlorides and dextrose to preserve the pH and the isotonicity.



More specifically, Privine HCL acts on the peripheral vascular bed by vasoconstriction. From the point of view of its use as a nasal vasoconstrictor, Privine HCL 0.1% is isotonic and possesses a pH 6.2. This is a pH value which approximates the pH of nasal secretions *in situ* in individuals with clinically normal noses. Experimental studies were undertaken to determine (1) its action on the cilia of laboratory animals, (2) its effect on the nasal pH of human subjects with acute rhinitides and acute rhino-sinusitis, and (3) its clinical effect on the nasal mucous membrane of individuals with nasal congestion, acute rhinitis, acute and chronic rhino-sinusitis, and allergic rhinitis.

Method. For the purpose of determining the relationship of this medicament to ciliary activity, 10 frogs and 4 dogs were employed. Ciliary action was studied in two sites—the bucco-pharyngeal mucous membrane of frogs and the tracheal mucous membrane of dogs. After bathing the selected sites in Ringer's solution to wash away blood and mucous secretions, the effect of Privine HCL on ciliary action was determined by evaluating the rate at which cilia lining the membrane carried a light object a given distance before and after application of a solution of the drug. Control tests were undertaken with normal saline, Ringer's solution, and Locke's solution. A solution of 0.1% Privine HCL was found to act favorably on ciliary activity and at no time appeared to be detrimental to it.

The relationship of Privine HCL to nasal pH was the subject of an investigation involving 10 human subjects. In his book, "The Technic of Medication," Fantus² asserts that a hydrogen-ion concentration near that normal to the mucous membrane is a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity. Elsewhere, Fabricant¹ has reported the use of a silver-silver chloride glass electrode in conjunction with the Coleman electrometer for the determination of nasal pH. This apparatus revealed that the pH of nasal secretions in contact with nasal mucous membrane in a clinically normal nose ranges from approximately 5.5 to 6.5. Intranasal instillations of Privine HCL 0.1% at no time disturbed the normal, physiologic pH values of the individuals observed who had clinically normal nasal passageways. In those individuals who had a slightly alkaline nasal pH, namely those with acute rhinitides and acute rhino-sinusitis, instillations of Privine HCL 0.1% reduced the alkaline nasal pH to a slightly acid level approximating the normal pH of the nose.

Over a 9 months period 104 human subjects were studied clinically, besides many others who have received the material occa-

sionally. In order to determine its value as a vasoconstrictor in conditions for which this type of medication is customarily prescribed, the Privine HCL 0.1% solution was tested on individuals with nasal congestion, acute rhinitis, acute and chronic rhino-sinusitis, subacute and chronic ethmoiditis, and allergic rhinitis. The method of application included the following procedures: instillation by means of the displacement method; instillation in the head-low posture; instillation into the paranasal sinuses; tampons; sprays; applicators; and as nose-drops for home use.

Of the series of 104 patients, 50 individuals with acute rhinitis were observed during the early stages at a time when engorgement of the nasal mucous membranes was a dominant symptom. In 25 of these patients, the medication was instilled into the nasal cavity with the patient either in the head-low posture or in the displacement position. In the remaining 25 individuals, tampons saturated with the Privine solution were placed in the nose for a period of 20 minutes while the patient was exposed to an infra-red lamp. Displacement therapy was instituted in a group of 25 patients with residual rhino-sinusitis following acute nasal infection, chronic rhino-sinusitis, and subacute and chronic ethmoiditis. In 15 patients the medication was instilled into the maxillary sinus following irrigation, and in the remaining patients of the series, 14 in number, the Privine solution was employed both in cases of allergic rhinitis and during the course of postoperative nasal treatment.

The Privine HCL solution proved to be an effective nasal vasoconstrictor when used in individuals with acute rhinitis. The action observed after spraying the nose and during the enumerated methods of application is that of decongestion. The nasal mucous membrane shrinks satisfactorily and this action exists for fully as long a time as that produced by solutions of ephedrine in physiologic saline. On a number of occasions, the shrinking action appeared to last longer. Many patients seemed to prefer the Privine HCL to ephedrine and ephedrine-like nasal preparations which they had used for home treatment on other occasions. Employed as a displacement vehicle, the results obtained with Privine HCL were as satisfactory as those obtained with ephedrine in physiologic saline. Instillation into the paranasal sinuses following irrigation, however, produced no apparent changes in the status of the sinus infection.

When instilled into the nasal cavity, when sprayed or inserted as tampons, solutions of Privine HCL 0.1% appeared to be free from local mucous membrane side-effects such as tingling, smarting and burning. The toxic side-effects sometimes ascribed to overdoses of ephedrine in physiologic saline, namely, apprehension, insomnia, tremor, cardiac palpitation, urinary retention and skin eruptions, were not observed in any of our series of 104 patients.

Summary. A 0.1% solution of Privine HCL is isotonic and has a pH of 6.2. It is a non-toxic nasal vasoconstrictor which is not

detrimental to ciliary activity, and its pH approximates the normal nasal pH of the human being. Its use in rhinologic practice has been entirely satisfactory in our hands.

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THE USE OF HEXENE-OL IN BURNS OF LIMITED AREAS

By BENJAMIN LEVINE, M.D.

MT. SINAI HOSPITAL, CLEVELAND, OHIO

(From the Department of Dermatology and Syphilology)

HEXENE-OL (C_6H_9OH) is a fatty alcohol derived as an oxidation product of hydrocarbons and was discovered in the development of synthetic rubber. This product is a light brown, semitranslucent, solid, fatty, soft substance with a melting point of 75° F. It is non-irritating and non-toxic. Friction or stirring changes melting Hexene-ol from a light brown to a light cream color. On solidifying this light cream color will last until the product is melted again. Hexene-ol was used both as a stearified substance with 1% zinc stearate and in its natural state. The therapeutic results were the same with the plain and the stearified Hexene-ol. This study comprises the use of Hexene-ol in regional burns and does not include burns that produce shock. It was not feasible to make comparative studies with other current methods for treatment of burns at this time.

Applied to the normal skin, Hexene-ol produces an increased localized perspiration over the area covered. In this respect it resembles histamine. The warmer the room temperature, the more profuse the localized perspiration becomes; it drips from the medicated area, even though the surrounding skin may be comparatively dry. It does not produce hyperemia. The increased perspiration is caused by direct stimulation of the sudoriferous glands or by stimulation of the sympathetic nerve fibers. The amount of perspiration produced is variable in different individuals, being greater in some than in others.

Prior to the use of tannic acid,³ gentian violet¹ and other dyes,² and more recently sulfadiazine,⁴ fatty, oily, greasy and waxy substances had been in wide use. All of these substances form an occlusive dressing and in this manner reduce the pain caused by a burn. Hexene-ol has an analgesic effect that goes beyond the stage produced by mere application of an oily substance to the burned skin. The pain is relieved in from 1 to 15 minutes after the application of Hexene-ol—usually less than 5 minutes. The healing is

unusually rapid and scarring is reduced to a minimum. None of the burns became secondarily infected after the application of this drug.

Most of the burns treated with Hexene-ol in this study were those sustained in industrial plants. In one plant, 150 burns were treated. The patients were maintenance men and foundry men. The sources of their burns were hot metal, hot rivets, hot gears, hot or boiling water, hot oil, steam pipes, soldering irons, hot solder, etc. The majority of the burns were either first degree or first and second degree burns. Two of the men had third degree burns—one on his foot from a white hot rivet, the other over all of his right forearm from a hot gear. The first degree burns cleared up in 24 to 48 hours. The second degree burns were cured in 5 to 7 days. The third degree burns took 14 to 18 days. None of them lost any time from their work. In all of these cases, Hexene-ol was applied immediately after the burn was sustained. The relief from pain was almost immediate—to within 5 minutes from the time of application. The incident of second and third degree burns was considerably less after the application of this drug than was the case when a proprietary burn ointment was used. Hexene-ol prevented undue damage to the burned skin, and many burns remained first degree that might otherwise have become second degree burns. Oil, grease and often grime were removed by the Hexene-ol when applied to the burned areas.

In another industrial plant, 6 maintenance men had 32 burns in a period of less than 2 years. Here the causes of the burns were steam pipes, hot water, hot solder and soldering irons. These burns previously were usually second and third degree in character and the burned areas would take 2 to 4 weeks to heal. The men carried a jar of Hexene-ol in their work kits. The drug was applied immediately after the burn was sustained. This invariably prevented blistering. Healing occurred in 24 to 48 hours. Here also the second degree burns were healed in 5 days to 1 week. One of the men slipped and his right arm was immersed to the shoulder in a vat of hot water kept at a constant temperature of 190° F. By the time he had pulled his work shirt off there were several blisters on the arm and it was red from the shoulder to the fingertips. The pain was relieved in less than 5 minutes after application of Hexene-ol. He was back at work within $\frac{1}{2}$ hour. The next morning the erythema was completely gone. The vesicles had healed within 1 week. Here also no time was lost from work except $\frac{1}{2}$ hour by 1 man. In this plant, Hexene-ol is now preferred to the other burn ointments which had formerly been used.

The drug was placed in the kitchen of a large restaurant and was used by the chefs. During the observation period, 6 of the men suffered 8 burns. These were obtained from boiling soups, hot grease, hot pans and skillets, and in 1 case from a book of safety

matches. The majority of the burns were on the hands and forearms, most of them fairly extensive. In 1 case both forearms were involved. Healing of all the burns took place in 3 to 10 days. There was no blistering—merely peeling without scar formation. In the case of the burn with safety matches, the left thumb and its interdigital web were severely burned. The pain stopped in less than 1 minute after application of Hexene-ol, and the burn was healed in 4 days. At the end of 1 week there was slight peeling only.

Various burns were treated with Hexene-ol. One of these was sustained by a physician who picked up some glass equipment which he had constructed and which had been white hot but a few moments before. He burned his thumb and several fingers painfully. Hexene-ol was applied immediately. The pain was relieved within 5 minutes. Peeling occurred 1 week later. There was no scar.

Another case was that of a colored woman whose face was splattered with hot grease. The burns were severe enough to cause loss of pigment in the burned areas. There was complete healing in 1 week. Two patients were burned by hot skillet handles, 1 by a hot furnace door and another by boiling water. The pain in all of these was relieved within 5 minutes and healing took place in 2 days. One woman, while pouring hot molten lead into a mold, spilled some of it on her foot, sustaining a third degree burn. This was completely healed in 2 weeks. Another woman sustained first, second and third degree burns on the dorsum of her right thumb and wrist from a hot flat iron. In this case Hexene-ol was applied 4 hours after the burn was sustained. Pain was relieved in 10 minutes. The first degree burn healed in 24 hours, the second degree in 3 days and the third degree in 12 days. She developed a bright red papular dermatitis from the drug, which however cleared up in 5 days.

There was record of 15 burns treated in the hospital Emergency Room. I was able to get in contact with 10 of the 15 patients. One of these (the sulphuric acid burn) will be reported later under "chemical burns." Hexene-ol was applied to these patients 15 minutes to 24 hours after the burns were sustained. It took longer to relieve the pain in these patients, approximately 10 to 15 minutes, and slightly longer to obtain a cure than in those cases in which Hexene-ol was applied immediately. Three of them sustained their burns from gas exploding in their stoves on ignition. Two were first degree burns and the third had first and second degree burns. One was treated 1 hour after being burned and 1 hour later was back at work. The other was treated 24 hours after being burned. She was completely well in 2 days. The patient with first and second degree burns was cured in 8 days; there were no scars.

A bus driver removed the radiator cap of an overheated motor and suffered first and second degree burns on his right hand. These

were treated 1 hour later at the hospital Emergency Room. Healing was complete in 1 week.

Three infants were treated for burns. The first, 7 weeks old, had first and second degree burns on her right hand, back of scalp and interscapular region. The pain was relieved within 15 minutes. Healing was complete in 10 days. The second was a 10 months old infant who received first and second degree burns on his left cheek, right arm and chest from hot coffee. The pain was relieved in 15 minutes. There was peeling 1 week later and the burns healed leaving no visible scars. The third infant, 14 months old, was badly burned by hot fat spilled from a skillet. He received first and second degree burns on his scalp, face, right arm and hand. The vesicles were then ruptured and Hexene-ol was applied. The pain was relieved in 15 minutes. Two days later he was out of doors playing. He was cured in 9 days. Later he had no visible scarring.

A colored porter who tripped and fell while carrying a pail full of boiling water sustained first and second degree burns of his left arm and hand. Pain was relieved in 10 minutes after application of Hexene-ol. There was no visible scarring left in 2 weeks.

The last of the patients treated in the hospital Emergency Room sustained first and second degree burns on both hands and wrists and also his face from a blow torch explosion. He first applied a well-known proprietary burn remedy. When he had had no relief from the pain 1½ hours later, he came to the hospital for treatment. Ten minutes after the application of Hexene-ol the pain was gone. He returned to his work. One week later he removed the bandages. There are no visible scars left.

It was thought inadvisable to treat extensive and severe burns with Hexene-ol since the drug produces localized perspiration, and it was not known how much body fluid loss might occur. However, 2 patients with extensive burns were partially treated with the drug. The first of these patients was a young man who fell into a vat of boiling dye. He had first and second degree burns of face, shoulders, arms and legs. The first degree burns were treated with Hexene-ol. These cleared up in 2 days. The second degree burns were treated with alternate spraying of tannic acid and silver nitrate. Eventually this coagulum had to be removed because of infection under it.

The second patient was a negro who received second and third degree burns from the explosion of a blow torch. The burns involved his face, both arms and the left thigh. Hexene-ol was applied to his face and right arm, which had second and third degree burns. The left arm and thigh had third degree burns and were treated with frequent and alternate spraying with tannic acid and silver nitrate. The face and right arm were healed in 2 weeks. The left arm and leg had eventually to be skin-grafted. Since the burns of the left arm and leg were more severe than the right arm and the face, fair

comparison cannot be made. However, the case does show the efficacy of Hexene-ol in burns.

There was a third patient in the hospital who had sustained a third degree burn, 5 cm. in diameter over the right iliac spine. This was obtained from a hot water bottle 3 days prior to admission to the hospital for treatment of renal calculi. Hexene-ol was applied 1 week after admission to the hospital, when other remedies had failed to promote any healing. The burn was healed 8 days later. The subsequent scar looks more like vitiligo than like a scar due to a burn.

Chemical Burns. Two patients burned with sulphuric acid were treated with Hexene-ol. One of them had his face splattered with boiling sulphuric acid. The acid was washed off with water and he was treated with Hexene-ol 15 minutes later in the hospital Emergency Room. The pain was relieved in 10 minutes and the lesions peeled for 10 days. No visible scars were left. The other patient was a boy of 13. He was riding home on his bicycle with a bottle of sulphuric acid in his pocket; the stopper came out and the acid spilled, burning his leg from groin to knee. The acid was washed off with water and Hexene-ol was applied. Within 4 days an ulcerated area $7\frac{1}{2}$ by 10 cm. was left on the anterior surface of the thigh. The rest had healed. The ulcer was healed in 3 weeks, leaving a smooth, soft, flexible scar that 1 year later is scarcely visible.

There was 1 burn from caustic soda that was healed in 24 hours. Another burn from hot resin was healed in 2 days. There also was a burn from glacial acetic acid which was present for 3 hours before being detected. This was cured in 3 days.

Burns From Carbon Dioxide Ice. I treated 2 infants, 7 and 9 months of age, who had cavernous vascular nevi, with CO₂ ice. Thirty seconds of light pressure produced vesiculation on each of these infants. Then each of them had 3 more applications of CO₂ ice, using light to moderate pressure 30 seconds, as in the first instance, but immediately after the treatment with CO₂ ice, Hexene-ol was applied. The mothers were instructed to continue to apply Hexene-ol twice a day. This completely prevented vesiculation. The burned areas peeled for 1 week to 10 days. There was no subsequent pain or restlessness on the part of the child. The cosmetic results were very good. However, in the case of an adult who had numerous lesions of senile keratosis on both hands, Hexene-ol did not prevent vesiculation when CO₂ ice was applied with firm pressure for 60 seconds, but there was no pain and the lesions healed in 10 days.

One patient had a wart 8 mm. in diameter removed by short wave cautery. The resultant ulcer healed in 10 days with application of Hexene-ol. This patient developed a dermatitis from the drug, which was cleared up in 3 days.

Sunburn. The results obtained by using Hexene-ol in sunburn were very satisfactory. A total of 14 patients were treated for this type of burn. One of the patients was burned through over-exposure to an ultra-violet lamp. Most of them were severely burned, over two-thirds of the body surface being involved. Several of them had vesiculation. The pain and burning sensation were relieved in 10 minutes after application of Hexene-ol. Two of the patients did not use the drug until 2 days after they were sunburned. Both were bedridden, 1 with crusted lesions on his back from ruptured vesicles. Both had used proprietary and semiproprietary burn remedies without results. Both had complete relief in 10 minutes and resumed their work the next day. The skin of the patients with the vesiculated lesions took 1 week to return to normal. The others took 2 to 4 days. One patient used Hexene-ol as a preventative against sunburn. Since his skin never tanned, but always became a bright, fiery red on exposure to the sun, he had to limit the time spent bathing at southern beaches to very brief periods. By applying Hexene-ol before going to the beach, he was able to spend a greater part of the day there without any ill-effects.

Summary and Conclusions. A series of 238 burns treated with a new drug, Hexene-ol, was observed and reported. Included were 14 cases of sunburn, 6 chemical burns, 8 carbon dioxide ice burns and 1 burn from a short wave cautery.

It was found that (1) when Hexene-ol was applied soon after the burn was sustained, vesiculation was prevented; (2) the relief from pain was prompt and lasting, although the drug does not produce a local anesthesia; (3) the healing was rapid and compared favorably with any preparation used by us in the treatment of burns; (4) secondary infection was prevented; (5) the incident of irritation from the drug was moderate, being less than 1% in this series.

Hexene-ol is particularly recommended for burns of limited areas, especially those incurred in industry and household. In our experience it is the best medicament to use in these cases. It is also of value in sunburn. Further investigation must be undertaken before its value can be determined in extensive burns accompanied by shock.

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BOOK REVIEWS AND NOTICES

HEMOLYTIC SYNDROMES. By WILLIAM DAMESHEK, M.D., TIBOR J. GREENWALT, M.D., RUSSELL J. TAT, M.D., and CAMILLE DREYFUS, M.D. A reprint of an exhibit sponsored by the New England Medical Center, Boston, Mass. Presented at the 1942 Convention of the American Medical Association, Atlantic City, June, 1942. Awarded Certificate of Merit for correlation and presentation of facts. Pp. 45. Privately printed. Price, \$1.50.

THIS is a graphic reprint of the authors' exhibit at the A. M. A. convention last June, which well deserved its award of a Certificate of Merit among the exhibits correlating the facts of medicine and science. With the present magazine and newspaper training of the public in the rapid appreciation of a topic through the medium of graphic presentation, a publication of this kind should be useful in leading to a better comprehension of this rapidly developing field of hematology by many of our profession who are repelled by the less efficient "selling methods" of scientific textbooks and journal articles.

Some 40-odd graphs and lists are offered, illustrating the various types of hemolytic anemias and their mechanisms. This group, that has studied and written extensively on this subject, can speak with authority. We fear, however, that some of the new categories set up will not only prove confusing but may not all stand the test of time. Also, one more page, by way of introduction, would have improved what is obviously an excellent product, that we are very glad to have for reference and instruction. E. K.

A HANDBOOK OF ALLERGY FOR STUDIES AND PRACTITIONERS. By WYNDHAM B. BLANTON, M.A., M.D., LITT.D., Professor of Clinical Medicine and Chief of the Immunology Clinic, O.P.D., Medical College of Virginia, Richmond, Va. Pp. 182; 20 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.00.

THE object of this brief volume is stated to be the assembling of material, representing a condensation of the subject of allergy as taught and practised today, to meet the needs of busy students and busier practitioners of medicine. This alone is noteworthy.

The introductory chapter on "The Fundamentals of Allergy" presents the principal theories of the allergic concept, important definitions, a brief historical sketch, influence of heredity, incidence, and a brief description of the management of the allergic patient. Subsequent chapters proceed in logical sequence and in more detail to discussions of the causes of allergy (inciting agents), resulting manifestations, with particular emphasis on the more common symptom complexes, and suggestions as to therapeutic approach and prognosis.

In general the subject matter is well presented, concise, and to the point, with a minimum of theoretical discussion. However, the chapter on "Gastrointestinal and Other Allergies" is rather too brief and sketchy in view of recent advances. Genitourinary allergy, particularly, is summarily dismissed with a brief description of possible symptomatology and the suggestion that foods of proven etiologic significance must be avoided.

Praise must be forthcoming for the useful bits of information contained in the "Appendix," wherein one finds instruction as to the preparation and

maintenance of a dust-free room, suggestions as to the avoidance of antigenic common foods, valuable recipes, and other practical hints.

This handbook should prove one of the most useful and practical thus far presented in the field of allergy. It is recommended.

M. M.

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE. By WESLEY W. SPINK, M.D., F.A.C.P., Associate Professor of Medicine, University of Minnesota, Medical School. Second Edition. Pp. 374. Chicago, Ill.: The Year Book Publishers, Inc., 1942. Price, \$3.00.

THIS book is a broad review of the subject of sulfonamide therapy with particular respect to the practical considerations involved in its use in medical and surgical infections. The author is to be congratulated on the timeliness of this second edition, which includes extensive consideration of sulfadiazine, the compound most recently to have found a place in general use. In the text the author makes only passing references to experimental studies, but interprets the results of these studies in terms of practical therapy. There is a comprehensive bibliography at the end of the book which should serve as a useful guide to the literature up to June, 1942. The book covers quite adequately the subject matter implied in the title and is certain to be a useful addition to the library of general practitioners and medical students. Individuals desirous of thorough acquaintance with the use of sulfonamides in specialized fields of practice will be able to use the bibliography as a guide to the current literature.

J. L.

SHOCK, ITS DYNAMICS, OCCURRENCE AND MANAGEMENT. By VIRGIL H. MOON, A.B., M.Sc., M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Pp. 324; 36 engravings. Philadelphia: Lea & Febiger, 1942. Price, \$4.50.

IN this book Dr. Moon has condensed the material incorporated in his first work on shock and has added a second part on the prevention, recognition and management of this condition. As in his earlier work, he has given an admirable concise account of the capillaries as they are affected by physiologic and pathologic conditions. To his former definition of shock as "a disturbance of fluid balance resulting in a peripheral circulatory deficiency which is manifested by a decreased volume of blood, reduced volume flow, and by progressive hemoconcentration," he has added "and by renal functional deficiency." One may be impelled to ask "and why not by functional deficiency in other organs as well, such as, for example, the liver?"

Dr. Moon is a strong advocate of the "traumatic toxemia" theory of the etiology of shock and it is therefore not surprising that a major portion of the first part of the book is devoted to an exposition of this concept. To the Reviewer it seems that too little attention is given to the significance of loss of blood and plasma at the site of injury and the reduced circulation which results from nervous reflexes.

The second part of the book is devoted to considerations of a practical nature. The author's viewpoint is strikingly displayed when he states "no factor in the *prevention of shock* exceeds in magnitude of importance the *prevention of absorption*." This statement has been considered thoughtfully and it is no exaggeration." This point of view is an interesting one, although it probably is not shared by the majority of those who have devoted themselves to the study and treatment of this condition.

In regard to the criteria of shock, Dr. Moon points out well that a fall in blood pressure is not useful as an early sign of oncoming shock. He maintains that hemoconcentration is the most valuable criterion. Only passing mention is made, however, of cyanosis, cold extremities or sweating. The final chapter is devoted to the use of blood, plasma and blood substitutes.

The volume is well printed, has an excellent index and a bibliography of over 400 references.

N. F.

DISEASES AND INJURIES OF THE LARYNX. By CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Honorary Professor of Broncho-esophagology, Temple University, Philadelphia, and CHEVALIER L. JACKSON, A.B., M.D., M.Sc. (MED.), F.A.C.S., Professor of Broncho-esophagology, Temple University. Second Edition. Pp. 633; over 200 illustrations, including 11 plates in color. New York: The Macmillan Company, 1942. Price, \$8.00.

THE student or practitioner who wishes detailed information relative to all conditions affecting the larynx will find this data in this book. The text and illustrations are of the usual high standard found in all Jackson publications.

K. H.

HOW TO LIVE IN THE TROPICS. By VIRGINIA LLOYD HUNT. Pp. 178, many tables. New York: Harcourt, Brace & Co., 1942. Price, \$2.00.

THIS handbook for travelers and prospective residents in the tropics is largely a re-hash of other publications, half understood and uncritically accepted by the author. It deals superficially with every imaginative phase of traveling and living in health and in sickness, with just enough application to the special conditions imposed by the tropics to justify its title. The most helpful part of the book is the bibliography.

E. W.

FLUORINE AND DENTAL HEALTH. Edited by FOREST RAY MOULTON; Publication No. 19; pp. 101, many figures and charts. Washington, D. C.: American Association for the Advancement of Science, Smithsonian Institute, 1942. Price, \$3.00.

BECAUSE of the widespread and increasing interest in the subject matter of this monograph, its appearance is most timely. The ground covered is indicated by the table of contents: Mottled Enamel: Early History and Its Unique Features (Frederick S. McKay); Geographical Distribution of Endemic Dental Fluorosis (Mottled Enamel) (H. Trendley Dean); The Chemistry of Fluorine as Related to Fluorosis (H. V. Smith); The Investigation of Physiological Method (H. Trendley Dean); Experimental Dental Fluorosis (Isaac Schour and Margaret Cammack Smith); Removing the Stain from Mottled Enamel (Harold B. Younger); Review of the Dental Fluorosis Studies at the University of Minnesota (Wallace D. Armstrong); Fluorine and Dental Caries with Special Reference to *L. acidophilus* (Philip Jay); Résumé of the Fluorine-Caries Relationship (Gerald J. Cox and Margaret Matuschak Levin); Fluorosis Studies at the University of Rochester (Joseph F. Volker); and Mottled Enamel from the Standpoint of the Public Health Dentist (including the relation of fluorine to dental caries in Illinois) (Charles F. Deatherage).

The significance of these studies is twofold. First, the etiologic relationship of fluorine to mottled enamel, when present, particularly in drinking water in excess of a certain critical level, presents a problem which can be

met only by public health methods. (The general practitioner of dentistry, however, will be interested in the chapter by Dr. Younger.) Second, the possibility that by the suitable application of soluble fluorides it will be possible to control or prevent dental caries, at once awakens and holds the interest of all those engaged in combating this most common of all diseases.

The book is well edited, illustrated and printed, and the format is gratifying. Unfortunately, no index is present.

All in all, this is a book of which dentists may well be proud and which can be heartily recommended to all dentists and to public health workers interested in dental problems.

J. A.

MEDICAL PROGRESS ANNUAL. Vol. III, 1942. A Series of 52 Reports on the Recent Accepted Advances in Diagnosis and Treatment Published During 1941 in the New England Journal of Medicine. Managing Editor, ROBERT N. NYE, M.D. Pp. 678. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

THIS volume follows along the lines of its predecessors in its inclusion of 52 different topics of general medical interest. The variety of subjects is great, including, in addition to many related topics under general medicine and some on general surgery, various odds and ends, such as Aviation Medicine, Dermatology, Anesthesia, Radiation Therapy in Gynecology. Medical Aspects of Obstetrics, Neurosurgery, Surgery of the Sympathetic System and War Medicine. Quite a long list, designed to apply to a variety of tastes.

For the most part the articles are of sufficient length to give the important features of the subject considered, and each one has a list of references, allowing for more detailed study, if desired. Shorter reviews of this sort have a definite value, differing from the longer, more comprehensive ones that appear.

H. M.

THE PLEURO-SUBPLEURAL ZONE. By J. SKLADAL, Reader in General and Experimental Pathology, Caroline University, Prague; Head of the Chest Department, Bulovka Hospital, of the City of Prague; Consulting Physician, the Masary, Institute for Treatment of Lupus, Prague-Motol. Pp. 103; 11 plates. Cambridge: The University Press; New York: The Macmillan Company, 1942. Price, \$2.75.

THIS is an excellent little monograph of 100 pages by a leading Czechoslovakian physician now a refugee in England. It is concerned with the pathology and diagnosis of disease localized to the pleura and adjacent shell of lung 2 cm. or so in thickness. The author believes that respiratory infections often consist of inflammatory changes in this zone which will be entirely overlooked unless special methods are used to detect them. Inasmuch as incipient tuberculosis may first be manifest by a so-called corticopleuritis, accurate examination of this outer portion of the lungs is essential.

Diagnosis is considered under two headings, physical and radiologic. Dr. Skladal describes a new method of auscultation, that of examining the patient after sudden forced expiration, as a specific means of detecting disease in the pleuro-subpleural zone. The mechanics of forced expiration are similar to those existing after cough, without the side effects of violent muscular activity. When even a thin strip of pulmonary consolidation exists beneath the pleura, sudden forced expiration results in an audible reduplication of the expiratory sound. This peculiar phenomena has been traced to secondary eddies in the air column at the rima glottis, which are buffered by air containing alveoli, but transmitted to the thoracic surface as a faint sound immediately following the usual sound of expiration, when

even a small strip of peripheral pulmonary tissue is consolidated. By the same mechanism, after sudden forced expiration, very fine postexpiratory showers of râles may be heard where consolidation in this subpleural zone is breaking down.

The radiographic appearance of disease in the corticopleural zone of the lungs varies from well-defined clouding of large portions of the lung fields, usually upper half, to a very faint, diffuse veiling of the lung fields that is easily overlooked. Indeed, while a well-developed corticopleurisy may show both the typical auscultatory phenomenon of the reduplicated expiratory sound, and the clouding in the roentgenogram of the lungs which the author refers to as "sugar icing on cakes," it is perfectly possible for disease in the outer zone of the lungs to exist with only one of these criteria fulfilled. The physical examination and the radiographic study thus become complementary rather than supplementary, one to the other. While this is true in all lung pathology, it is especially so where only the outer layer of lung and pleura are affected.

This little book will receive some criticism from the English or American reader because of its style. Even though written directly in English it often reads like a rather literal translation from the German. Many words and phrases will be found to have an odd relation to their context, and this may prove somewhat disturbing to the casual observer. In addition, there are many unnecessary repetitions and the entire effect is that of rendering a simple exposition in a somewhat involved and redundant manner. Be that as it may, the author's contribution is a valuable one and should be read by all students of chest disease.

R. B.

CEYLON, Exorzismus und Heilkunde. By PAUL WIRZ. Pp. 292; 56 figures and 87 plates. Bern, Switzerland: Verlag Hans Huber, 1941. Price, 18 Swiss francs.

DURING a 5-year stay in Ceylon, the author had opportunity to learn at first hand, by word of mouth, and by observation, the medical ceremonies and exorcisms of an ancient people, the Singhalese, who have lived unchanged for 5 centuries under the dominance of three different powers. Though by no means a primitive people, they appear to be as completely under the sway of unseen powers and demonic enemies as any barbarous tribe, but differ in possessing a highly developed system of magic, exorcisms and astrologic wisdom, largely committed to writing.

The book is well illustrated and obviously prepared with care and erudition. It will be of more value to students of ethnology and folklore than to medical historians, though the latter will also turn to it with profit if working in this field. The text will not appeal to the casual reader.

E. K.

A MANUAL OF EXPERIMENTAL EMBRYOLOGY. By VIKTOR HAMBURGER, Department of Zoölogy, Washington University, St. Louis, Mo. Pp. 213. Chicago, Ill.: Chicago University Press, 1942. Price, \$2.50.

THE author of this manual was associated for many years with one of the most outstanding modern experimental embryologists, Prof. Hans Spemann. The directions, therefore, especially those used in amphibian material and chick material, are based upon long-effective experience. The procedures of technique are well illustrated and explained, and have been used for a number of years in the author's classes, containing graduates and undergraduates. The students are oriented in each experiment by a discussion of the significance of the experiment, a very helpful asset.

Parts I and V cover equipment and instruments, sources and care of

animals, a long list of experiments on amphibia, chick regeneration and the gradient theory. A bibliography follows each division and subdivision of experiments. A plan is also submitted for a one-semester course, and the book is well indexed. An Appendix contains reports of Harrison's well-known Amblystoma, Pollister and Moore's *Rana silvanica* and Shumway's *Rana pipiens* stages.

C. P.

THE HORMONES IN HUMAN REPRODUCTION. By GEORGE W. CORNER, M.D. Pp. 265; 32 figures, 24 plates. Princeton, N. J.: Princeton University Press, 1942. Price, \$2.75.

THIS is an elaboration of lectures delivered at Princeton University to a general audience. Three chapters are devoted to explanations of anatomy and physiology for those who are unfamiliar with cellular biology. The subject matter, however, is sufficiently technical to be of interest to the trained scientist; and the physician who is not a laboratory investigator should find it useful as a lucid description of research endocrinology. He will also gain from it many interesting facts in comparative physiology, and obtain historical perspective of the development of our knowledge of sex hormones.

The manner of presentation is very pleasing, almost colloquial, yet dignified. The illustrations are simple and effective. Often the text is enlivened by accounts of the drama of research. Altogether it is an unusually successful presentation of scientific intricacies to a lay audience, without sacrificing accuracy.

I. Z.

CHANGES IN THE KNEE JOINT AT VARIOUS AGES. By GRANVILLE A. BENNETT, M.D., Associate Professor of Pathology, Harvard Medical School; HANS WAINE, M.D., Research Fellow in Medicine, Harvard Medical School; Graduate Assistant in Medicine, Massachusetts General Hospital; and WALTER BAUER, M.D., Associate Professor in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital; Director, Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases. Pp. 125; 31 plates. New York: The Commonwealth Fund, 1942. Price, \$2.50.

THIS is an interesting and stimulating book on the development of degenerative joint disease. The authors studied the knee joints of 63 individuals, ranging in age from 1 month to 90 years, obtaining their specimens by post-mortem or following amputation, and no joint abnormalities had been observed previously on physical examination. The authors give a careful description of the anatomic changes that were found in these knees by decades, and feel that in every subject beyond the age of 15 some degeneration of the joint was observable. The bone changes affected all of the articulating surfaces, especially the patella, and were demonstrated by a dulling of the articular cartilages, fibrillation, visible fissures with roughening, fraying or splitting of the surface or more severe and extensive changes of the bony, cartilaginous and fibrocartilaginous joint components, while changes in the synovial membrane were consistently less advanced. The grossly visible alterations throughout the synovial membranes were relatively slight, and occurred during the later decades.

As the degenerative process advanced, grossly visible marginal proliferations are described as due to certain definite structural and functional characteristics of the border zones between articular cartilage and synovial lining tissue.

The authors think that an infectious cause of degenerative joint disease is entirely lacking, and that the highly important advanced age factor has

not been taken sufficiently into consideration, advancing age being the most constantly observed single factor.

They conclude that there are two fundamental considerations applicable to every example of degenerative joint disease: "One is the disadvantageous biological position of articular cartilage when subjected to injury and the other concerns the effect of mechanical stress and strain incident to joint function upon a tissue whose specific means of resistance to such use has been depleted. Further investigation in a degenerative joint process should be a combination of microscopic observation with histo-chemical methods and studies in tissue metabolism." P. C.

MENTAL ILLNESS: A GUIDE FOR THE FAMILY. By EDITH M. STERN with the collaboration of SAMUEL W. HAMILTON, M.D. Pp. 134. New York: The Commonwealth Fund, 1942. Price, \$1.00.

THE aim of this much needed book is set by the Dedication: "To the thousands of anxious men and women who have mentally ill relatives, in the hope that they will find some comfort and practical guidance in these pages." Written by one of the laity, for whom the point of view of the family and the patient is more easily preserved than for the professional, whether the specialist or the distracted general practitioner, this book will do much to guide through a harassing experience, which unfortunately is said sooner or later to strike one family in five in this country. When intelligently read and reread, it should save much unnecessary suffering for those concerned. Its 18 short chapters consider the proper attitude toward mental illness of all kinds, explain the why and wherefore of the physician's advice, why hospitalize if this should be necessary, what will happen there, and what should be done when the patient is discharged (as happens to the vast majority).

Executed with the customary excellence of Commonwealth Fund production, this concise booklet will be of great service to all who have to cope with the problems of mental illness, and an inestimable boon to the families of this much misunderstood class of patients. E. K.

AN INTRODUCTION TO MATERIA MEDICA AND PHARMACOLOGY. By HUGH ALISTER MCGUIGAN, Ph.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois, College of Medicine, Chicago, and ELSIE E. KRUG, B.S., R.N., Science Instructor, St. Mary's School of Nursing, Rochester, Minn. Third Edition. Pp. 779; 46 illustrations and 37 color plates. St. Louis: C. V. Mosby Company, 1942. Price, \$3.50.

This text is designed for nurses, being a revision of Brodie's "Materia Medica for Nurses." The first portion, dealing with pharmacy, weights and measures, administration of medicines and dosage, is well presented and valuable for the student or graduate nurse. The remainder of the book is devoted to the pharmacology of special systems (nervous, autonomic nervous, digestive, circulatory systems, etc.). These 550 pages are too much and yet too little: too much because there is scarcely room in the nursing curriculum for the details presented, and too little because more time might be spent profitably upon the experimental methods of pharmacology, the ways in which drugs modify physiologic processes and the special significance of drug actions to nurses.

The book contains many fine illustrations; however, 23 of the 37 color plates portray plants from which drugs are derived and, though time-honored illustrations, seem to have little place in this book. J. C.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. A. *General Survey, Drugs, and Critical Abstracts*. 1941-42. Under the General Editorship of SIR HUMPHRY ROLLESTON, B.T., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Some-time President of the Royal College of Physicians of London. Pp. 482. B. *Cumulative Supplement*. 1941-42. Under the Editorship of SIR HUMPHRY ROLLESTON. Pp. 289. London: Butterworth & Co., Ltd., 1942. Price, \$10.00 (U. S. A. funds).

THE general plan of this annual encyclopedia is similar to that of previous volumes. The first volume is "divided into 3 parts, which contain respectively a series of critical surveys of various branches of Medicine, a section dealing with new developments in drugs, and abstracts from current medical publications. . . ." Although it is considerably reduced in size from pre-war volumes, it contains the same excellent type of material. The Critical Surveys "consist of a series of authoritative, signed reviews dealing in general terms with the present position of some branches of medical science and practice, and indicating the possible future developments in these . . ." In the Drugs section, "new drugs, or modifications of old drugs, are discussed from their therapeutical and pharmacological aspects . . ." In the Abstracts of medical literature are brought together "the essentials of a large number of papers published throughout the year ending June 30, 1941, by British, American, and other authors. As a result of the wide extent of the War, the output of European journals and other medical publications has greatly diminished. . . ." The topics, never occupying more than a few pages, are conveniently arranged alphabetically, with the name in bold-faced type. Unfortunately, many are not up to date.

The Cumulative Supplement, which is the second volume of the pair for 1941-42, brings up-to-date the matter contained in the parent volumes. In this, also, the various topics are considered in alphabetical order; the name in bold-faced type, making them easily and quickly found.

E. K.

NEW BOOKS

The Hormones in Human Reproduction. By GEORGE W. CORNER, M.D. Pp. 265; 32 figures, 24 plates. Princeton, N. J.: Princeton University Press, 1942. Price, \$2.75.

Diseases of the Liver, Gallbladder and Bile Duct. By S. S. LIGHTMAN, M.D., F.A.C.P., Adjunct Physician, Mount Sinai Hospital; Assistant in Post-Graduate Medical Instruction, University Extension, Columbia University. Pp. 906; 122 engravings and a colored plate. Philadelphia: Lea & Febiger, 1942. Price, \$11.00.

Chemistry and Physiology of the Vitamins. By HANS R. ROSENBERG, Sc.D. Pp. 674; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, \$12.00.

Clinical Anesthesia. A Manual of Clinical . . . By JOHN S. LUNDY, B.A., M.D., Head of Section on . . . Clinic; Professor of Anesthesia, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota; Diplomate and Member of the American Board of Anesthesiology, Inc.; Member of the Subcommittee on Anesthesia, National Research Council. Pp. 771; 266 illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, \$9.00.

My Self, My Thinking, My Thoughts. By K. W. MONSARRANT. Pp. 140; a few figures. London: University Press of Liverpool, Hodder & Stoughton, 1942. Price, 7/6 net.

Hemolytic Syndromes. By WILLIAM DAMESHEK, M.D., TIBOR J. GREENWALT, M.D., RUSSELL J. TAT, M.D., and CAMILLE DREYFUS, M.D. A reprint of an exhibit sponsored by the New England Medical Center, Boston, Mass. Presented at the 1942 Convention of the American Medical Association, Atlantic City, June, 1942. Awarded Certificate of Merit for Correlation and Presentation of Facts. Pp. 45. Privately printed. Price, \$1.50. (See Review, p. 131.)

Nasal Medication. A Practical Guide. By NOAH D. FABRICANT, M.D., M.S., Associate in Laryngology, Rhinology and Otolaryngology, University of Illinois, College of Medicine. Pp. 122; 20 figures. Baltimore: The Williams & Wilkins Company, 1942. Price, \$2.50.

Handbook of the Lying-In Hospital. Woman's Clinic of the New York Hospital, 530 East 70th St., New York. Pp. 158. New York: Cornell Medical College Book Store, 1300 York Ave., 1942. Price, \$2.00.

This summary of instructions to medical students and interns includes: (1) Organization and duties of the house staff. (2) Organization of the out-patient department. (3) Social service. (4) Admission routine. (5) Routine for delivery and operating rooms. (6) Blood transfusions. (7) Routine laboratory tests. (8) Diets. (9) Analgesia and anesthesia. (10) Management of complications of pregnancy. (11) Routine and clinical application of various procedures.

The Editor, Dr. A. A. MARCHETTI, is to be complimented upon both contents and form, which includes excellent paragraph headings, and numbering of most of the lesser paragraphs, all making for ready reference. The book is recommended to obstetricians and gynecologists interested in the organization of departments of obstetrics and gynecology. D. M.

Love Against Hate. By KARL MENNINGER, M.D., with the collaboration of JEANETTE LYLE MENNINGER. Pp. 311. New York: Harcourt, Brace & Co., 1942. Price, \$3.50.

First Aid. Surgical and Medical. An Advanced Guide. By WARREN H. COLE, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine; Director of Surgical Service, Illinois Research and Educational Hospitals, Chicago; and CHARLES B. PUESTOW, B.S., M.S., M.D., Ph.D., F.A.C.S., Associate Professor of Surgery, University of Illinois College of Medicine and Graduate School; Surgeon, Illinois Research and Educational Hospitals; Senior Surgeon, Henrotin Hospital; Consulting Surgeon, Municipal Contagious Disease Hospital and Bethany Home and Hospital, Chicago, and St. James Hospital, Chicago Heights. Illustrations by CARL LINDEN in collaboration with TOM JONES of the Illustration Studios of the University of Illinois College of Medicine, Chicago. Pp. 351; 92 figures. New York: D. Appleton-Century Company, Inc., 1942. Price, \$3.00.

Designed primarily for medical students but supplied with simplified descriptions of anatomy and physiology to place it within the grasp of laymen, this volume is a practical, yet fairly complete, discussion of military and civilian emergencies. Unusually strong emphasis is placed upon what not to do, in every type of emergency as well as in a special chapter devoted exclusively to "don'ts." Many lucid diagrams are supplied. M. F.

Medical Clinics of North America. Symposium on Endocrinology. November, 1942. Vol. 26, No. 6. Pp. 342. Three-year cumulative index (Volumes 24, 25 and 26—1940, 1941 and 1942). Philadelphia: W. B. Saunders Company, 1942. Price, \$16.00 for the year.

Mental Illness: A Guide for the Family. By EDITH M. STERN with the collaboration of SAMUEL W. HAMILTON, M.D. Pp. 134. New York: The Commonwealth Fund, 41 East 57th St., 1942. Price, \$1.00.

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PROGRESS OF MEDICAL SCIENCE

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UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS

SOME CLINICAL ASPECTS OF RECENT VITAMIN ADVANCES

MUCH of the literature on the vitamins concerns problems which are not of clinical or therapeutic interest. The present review is concerned only with the more recent reports of primary clinical importance. No special emphasis has been given to the place of vitamins in pediatrics, ophthalmology, and otolaryngology, because these have been recently reviewed in the section on the Progress of Medicine.^{21,70,86}

General discussion of the approach to therapy and the use of purified and synthetic vitamins has no place in this review. A general evaluation of these phases of nutrition is well discussed in textbooks⁴⁹ on treatment. However, certain of these aspects are now in the process of clarification, as exemplified by the report of the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association.⁵⁹ These groups, working together, pointed out the fact that the general practice of industrial concerns of providing all their employees with vitamins indiscriminately is misguided. When a satisfactory study of a given industrial situation indicates the wisdom of providing vitamins for employees, the necessity for observing proper scientific limitations of such action in the particular situation is important. After an employee has been restored to a good nutritive state, the use of a good diet of natural protective foods thereafter should suffice. The Councils further indicated that nothing in their report was intended to belittle the significance of vitamins in nutrition or the value of proper use of added vitamins in improving staple foods, such as bread and flour. The purpose of the report was to discourage indiscriminate mass use of vitamins.

Vitamin A. The value of diagnostic tests in the detection of vitamin A deficiency remains a debated question. The feeling is prevalent that the standards for the photometer test are too high. Prolongation of adaptation time occurs with little apparent clinical or diagnostic significance and photometer tests do not always correlate well with blood levels.¹³ Still the photometer has been found useful in diagnosis, particularly when determinations are made before and after treat-

ment.^{12,27b} Similarly, although evidences of deficiency do not correlate accurately with vitamin A blood levels, normal values are not likely to occur in clinical deficiency.

A more recent addition to tests for vitamin A deficiency is biomicroscopy under slitlamp illumination. Kruse,³⁶ using the method on 143 persons in the low income bracket, found gross (Bitot's spots) and microscopic lesions of xerosis conjunctivæ in 45% and 54%, respectively. These he considered evidence of vitamin A deficiency and suggested that they might precede the development of night blindness. However, Berliner⁶ does not consider these changes necessarily pre-xerotic states related to vitamin A metabolism, and Callison¹⁰ has described vitamin A deficiency and disturbed dark adaptation without changes in the conjunctiva. Obviously, the problem requires further evaluation.

Recent work suggests that variations in reactions to standard color-vision tests may not rest entirely on Mendelian characteristics, but may be corrected with vitamin A.¹⁹

Sandels and associates⁶⁴ have described follicular conjunctivitis as a common manifestation of vitamin A deficiency, particularly in the age groups from 6 to 12 years. They have correlated these findings with low dietary intake, and have found 13,000 units of vitamin A daily effective in treatment.

Youmans⁹⁵ has pointed out that most vitamin A deficiency seen in practice develops secondary to some other primary disease. This is particularly true in liver disease, for important phases of the metabolism of vitamin A, for example storage, and the conversion of carotene into vitamin A, takes place in this organ. Cirrhosis of the liver,^{27a} as well as infectious processes, affect storage.⁵⁷ Blood levels of the vitamin are closely linked with the liver stores, where mobilization is influenced by sympathetico-adrenal stimulation.⁹⁸

Various infections, such as tuberculosis and osteomyelitis, increase the need for vitamin A. In tuberculosis,⁷ absorption of vitamin A is also poorer than normal. It has been found that the greater the weight loss and the more severe the gastro-intestinal symptoms, the poorer the absorption of the vitamin. Autopsy findings have not explained these results. Either decreased absorption or increased destruction is produced by various diarrheas, surgical procedures, and certain gastro-intestinal disturbances. In gastro-intestinal cancer, the levels of vitamin A in the plasma have been reported below normal in 86% of the patients examined.⁶² This is thought to result from both inadequate absorption and an hepatic dysfunction of storage or formation from carotene. In some patients, dietary deficiency or malabsorption could not explain the low values. Malignancies, other than those arising in the gastro-intestinal tract, may produce similar changes in the plasma levels.

Most interesting is the report on treatment of arterial hypertension⁵⁵ with vitamin A. Doses of 180,000 to 200,000 units daily, reduced later to 90,000 to 100,000 units, are reported to give a drop in blood pressure of 30 to 40 mm. of mercury. A later report from this country⁸⁷ confirms these results in experimental renal hypertension in dogs, but controlled observations in patients by Taylor, Corcoran and Page⁸⁴ do not support these results.

Vitamin B Group. Clinically, at least 8 well-known substances in the vitamin B complex must be considered. These are thiamin, niacin, riboflavin, pyridoxine, pantothenic acid, p-amino-benzoic acid, choline, and biotin. Only the first 3 are well established clinically. Experimental choline deficiency is characterized by fatty changes in the liver, and this substance is quite likely essential for man. The others are considered below.

Probable "safe" levels for daily intake of the B vitamins by human beings are variously stated. The National Research Council Committee on Foods and Nutrition⁹ suggests the following for a 70 kg. man using 2500 calories daily:

Thiamin, 1.5 mg

Niacin, 15 mg.

Riboflavin, 2.2 mg.

R. J. Williams^{92a} states that a fully adequate idea of the requirements of human beings for the various vitamins could presumably be obtained only as a result of a series of extended controlled studies using man. He compared the vitamin content of a well-rounded mixed diet, such as might be recommended for human beings, the vitamin content of certain commercial animal foods, and of the carcass of the rat. On an isocaloric basis, the vitamin content agreed closely. He estimated that "safe" levels for daily intake of B vitamins for human beings, even under conditions of pregnancy and lactation, are probably represented by: thiamin, 3.2 mg.; nicotinic acid, 40 mg.; riboflavin, 3.7 mg.; pantothenic acid, 11 mg.; biotin, 0.14 mg.; inositol, 1000 mg.; pyridoxine, 1.5 mg.; and folic acid, 1 mg. Although the last 4 are not definitely known to be required by man, they occurred in foods in about the extent indicated. These figures exceed those laid down by the National Research Council Committee in thiamin, niacin, and riboflavin. Estimates for pantothenic acid have not been made by others, and the same is true for pyridoxine, folic acid, and inositol.

R. D. Williams and his associates⁹¹ have estimated the optimal intake of vitamin B₁ at 0.5 to 1 mg. per 1000 calories in a diet in which the carbohydrate and fat have the conventional proportions. It should be emphasized that the thiamin content of the average American diet, as consumed by the middle two-thirds or three-fourths of the population prior to enriched bread and flour was about 0.8 mg. per 2500 calories.³⁸

Deficiency of the B vitamins, along with iron deficiency, is probably the most prevalent today. Their occurrence in the same foods emphasizes the common finding of multiple deficiencies in the same patient. In certain instances of cirrhosis of the liver, the importance of abnormalities of the diet, particularly in protein and B complex is becoming evident. In experimental animals,²⁶ a type of cirrhosis characterized by focal necrosis and fatty infiltration, occasionally developing into periportal fibrosis, has resulted from diets low in B complex and protein. These changes resemble those seen in alcoholic patients. The relationship of these factors to cirrhosis of the liver in man has just recently been admirably reviewed by Wilen.⁹⁰

Evidence is also beginning to accumulate to suggest a relationship between certain members of the B complex and the development of certain types of cancer. It is suggested that the most frequent, and probably the most important form of chronic irritation in the oral

mucous membrane, from the standpoint of cancerigenesis, is avitaminosis B.⁴⁵ The belief was stated that prophylaxis against mouth cancer would include an increase in general intake of vitamin B in foods. Relationships have also been shown between the B group and the development of experimental cancer of the liver in animals.⁶¹ The application of these data to the study of this disease in man is anxiously awaited.

Wernicke's encephalopathy,¹¹ which is characterized by ophthalmoplegias, clouding of consciousness, and ataxia, found in chronic alcoholism, gastric carcinoma, pernicious anemia, vomiting of pregnancy, and other conditions, has responded to treatment with B complex.

A relationship has been reported between the endocrine glands and the metabolism of vitamin B complex.³ Improvement has been noted in B complex deficiencies by the administration of anterior pituitary extracts when the clinical picture has not been entirely relieved by vitamin therapy. Also estrogen therapy has been noted to induce or exaggerate polyneuritis, pellagra, and cheilosis. Ashworth and Sutton³ suggest either an increased demand for, or a suppression of utilization of, the vitamin B complex by estrogens.

The success of B complex, either as crude extract or purified mixtures in multiple B deficiency, is well established. Spies, Grant and Grant⁷⁶ describe a mixture of 25% dried brewers' yeast, 67% peanut butter, and 8% peanut oil as a protective food in B deficiencies, particularly in pellagra, beriberi and ariboflavinosis. Patients taking 60 to 75 gm. of this mixture daily as a dietary supplement showed improvement in the appetite, gain in weight, and healing of lesions.

There are on the market many vitamin B complex preparations which represent extracts of yeast and liver. Such a source is no guarantee of potency for there may be large losses in extraction. It has been estimated^{92a} that to get enough of the B vitamins from such sources to equal the intake on a good diet, one would have to consume 10% of one's calories in the form of 7 to 8 teaspoons of the dry powder of one commercial extract tested. Many such preparations are fortified with thiamin, niacin, and riboflavin, but are not "balanced" in the amounts of the various components.

Vitamin B₁. Induced thiamin deficiency⁹¹ of severe degree is associated with states of inactivity, apathy, serious derangement of metabolic processes, loss of weight, and finally prostration. Moderate prolonged restriction was associated with emotional instability reflected by irritability and moodiness, quarrelsomeness, lack of cooperation, vague fears progressing to agitation, mental depression and other signs. Mental and physical inefficiency preceded other more objective manifestations of thiamin deficiency by weeks or months. Changes in judgment and foresight have also been noted.⁹¹

Clinical evaluation shows that about one-third of the wage-earning families of the population live on inadequate diets, a large part of which rests in the B group, and particularly thiamin. This, coupled with losses through cooking conditions, may lead to serious deficiency. In meats, a potent source, boiling and stewing may destroy up to 50% of the thiamin. Additional need for thiamin, or diseases interfering with intake, are likely to be associated with such deficiency. The diagnosis of beriberi is often masked in such diagnoses as diabetic, gesta-

tional, alcoholic, or metabolic polyneuritis. Pellagra, sprue, celiac disease, hyperthyroidism and febrile states may have, as part of their picture, thiamin deficiency.

Thiamin is normally excreted in appreciable amounts in the sweat.²⁸ It has been estimated that a man working in a room of moderate temperature may sweat 2 to 3 kg. daily without visible perspiration. This would account for loss of 5% to 15% of ingested thiamin.²⁸

Laboratory methods for estimation of thiamin subnutrition are not widely used clinically. This is due, in part, to a lack of simplicity as well as to variations in experimental results.²⁰ Total blood thiamin levels may not fall sufficiently early in deficiency to make them of value diagnostically in so-called "subclinical" states.⁹⁷ Excretion tests,⁴⁶ saturation tests, and pyruvate determinations on the blood before and after treatment have been reported as useful.

Increase in the thiamin content of the diet may be accomplished by the addition of thiamin-rich foods, lean meat, internal organs, milk and whole-grain cereals. Thiamin-poor foods may be eliminated. Enriching of basic foods in which processing has removed the thiamin content, is useful. Wheat flour and its products are estimated to contribute more calories to the American diet than any other class of food¹⁷ and, with refined sugar and fats, account for over one-half of the caloric intake. White bread is about one-tenth as potent in thiamin as whole wheat and there are marked reductions in calcium, iron, and other factors as well. The enriching of flour to the equivalent of whole wheat is an important step in correcting deficiency produced by such refining processes, but one cannot assume such flour is superior to, or even nutritionally equivalent to, whole-grain flour. One should not be lulled into a feeling of false security in his thiamin quota by eating bread made of enriched flour. Six slices of such bread supply a little over one-sixth of the daily requirement,¹⁷ so that other foods must be depended upon to complete the daily quota.

Thiamin has been used in the treatment of many seemingly unrelated conditions, some of which have already been mentioned. Reports of successful treatment of herpes zoster are not conclusive. Even injections locally into the areas about the eruption have been tried. Equivocal results are also reported in tic douloureux, pernicious anemia, morphine addiction and irradiation sickness. Combined with other factors in the B complex, and at times with vitamin E, it has been used in many neurologic states which are, in general, refractory to treatment. Diabetic neuritis of the symmetric type, particularly that starting in the lower extremities, has been successfully treated by oral doses of 10 mg. daily.²² Other types of pain, vague aches, and pain involving single nerves did not respond consistently.

Sensitization, including positive intracutaneous and passive transfer tests, to thiamin has been described.³⁹

Riboflavin. Since the association of riboflavin deficiency with a distinctive clinical picture in man, there has been wide interest in this problem. Attempts have been made to establish diagnostic chemical tests for early deficiency. Blood values are of little diagnostic importance,⁴ and excretion tests, as yet, are of little practical value. In early diagnosis, the recognition of the superficial vascularizing keratitis and its associated symptoms of burning, itching, blurring of vision remains

most important,⁸² for this finding is described as the earliest and most common visible manifestation. While changes in the tongue and lips generally follow the keratitis, absence of the latter does not exclude riboflavin deficiency. It is interesting to note also that interstitial keratitis associated with hereditary syphilis has responded more rapidly to treatment when riboflavin is given.¹⁴

It has been suggested,⁹³ because of the recognition of widespread ariboflavinosis, that destruction of riboflavin by light at the high temperatures used in cooking might be of practical importance. Up to 48% of riboflavin may be destroyed when food is exposed to light during cooking in open vessels. Williams and Cheldelin⁹³ showed that, under usual kitchen conditions in a well-lighted room, destruction of riboflavin in liquid foods was rapid and that opacity tended to slow up the loss. Certainly, large losses in such foods as milk and eggs which alone contribute approximately 40% to 50% of the riboflavin in the average American diet may aggravate any shortage.⁹³

Spies, Bean, Vilter and Huff⁷⁵ found ariboflavinosis to be common in children. It has been reported in the premature infant.⁷⁹ Nursing infants were satisfactorily treated by administering to the lactating mother 1 mg. doses 3 times daily or brewers' yeast or liver extract daily. Five mg. of riboflavin daily is usually adequate except in liver disease, gastric achlorhydria or diarrhea when the amount should be doubled to tripled. Sodium riboflavin may be given parenterally in 10 to 15 mg. doses.

Niacin. Recently the term "niacin" has been applied to nicotinic acid.¹⁵ More acute forms of nicotinic acid deficiency may give rise to clinical pictures unlike that of pellagra. Such is the so-called nicotinic acid encephalopathy characterized by clouding of consciousness, progressive stupor, cogwheel rigidity and gasping and sucking reflexes. Sydenstricker and Cleckley⁸¹ include in this group of symptoms such manifestations as lethargy, stupor, mania, hallucinations and disorientation which respond promptly to niacin therapy.

Many tests for niacin deficiency have been advocated. Blood and urine levels are of little help. There is a constant loss of at least 10 mg. of known nicotinic acid derivatives in the urine daily, regardless of diet.⁶⁶ The extra excretion of nicotinic acid and trigonelline after test doses of nicotinamide may serve as an indication of the nutritional status of an individual in respect to nicotinic acid,⁶⁶ but is not yet satisfactory as a clinical test.

The estimation of the amount of certain fluorescent substances in the urine shows promise as a test of nicotinic acid deficiency.⁵⁰ Evaluation of this test is not yet complete. One of the fluorescent substances, called F_1 , was found in relatively small amounts in normal urine but in larger quantities in the urine of pellagrins. Another substance, F_2 , developed fluorescence only on the addition of alkali. It was not found in the urine of pellagrins but reappeared after nicotinic acid therapy, and increased in the urine of normal subjects after administration of nicotinic acid. Animal experimentation, to obtain a purer form of nicotinic acid deficiency than occurs in patients, confirmed these results although the reciprocal relationship of F_1 and F_2 was not perfect.

Pyridoxine. Despite the fact that there is as yet no clear-cut evidence of the importance of pyridoxine in clinical nutritional defi-

ciency, the study of its metabolism in man suggests an important rôle.^{68,73} The similarity of its distribution in food to other members of the B group also suggests its importance, as does the work of Williams, quoted above.

Since the report⁷⁴ that administration of pyridoxine to 4 pellagrins on a controlled diet caused the disappearance of such symptoms as extreme nervousness, insomnia, irritability, abdominal pain, weakness and difficulty in walking, its use has centered on muscular and nervous disorders, including pseudohypertrophic muscular dystrophy, myasthenia gravis, amyotrophic lateral sclerosis, Parkinsonism and others. Jolliffe³³ found it beneficial in Parkinsonism of less than 3 years' duration and without a history of encephalitis. Still others report no improvement with pyridoxine in dosage varying from 50 to 100 mg. intravenously daily or every other day, alone, or in combination with vitamin E and other factors of the B complex. In pseudohypertrophic muscular dystrophy, reports are similar. Antopol and Schotland² found considerable improvement in 6 cases while Keith,³⁴ using 100 to 200 mg. intramuscularly found no improvement. There are many difficulties in the evaluation of such therapy.⁴²

Because of the reported relief of weakness in pellagrins by pyridoxine several studies have been carried out to test the effect of pyridoxine on muscular weakness. Muscular weakness brought to the point of exhaustion by performance of work has been relieved by pyridoxine in patients with neurasthenia, hyperthyroidism, and ulcerative colitis.⁶³ In these states, deficiency might be expected. However, in patients with severe malnutrition, tested in the same way, there was no positive response. In another report,²⁴ a study of fatigability carried out by the double work period method on subjects receiving "adequate" nutrition showed no immediate effect from thiamin, cocarboxylase, riboflavin and parenteral vitamin B complex.

Pantothenic Acid. The status of our knowledge of the importance of pantothenic acid in human nutrition is similar to that of pyridoxine. Its presence in all types of living cells^{92b} speaks for its importance, probably as a catalyst in some step of carbohydrate metabolism. In man,^{47,54,94} sufficient quantities occur in the blood for determination of blood levels, and the daily urinary excretion has been measured. Again, these facts indicate the entrance of this vitamin into the human economy. Further suggestions that pantothenic acid may be of clinical importance is the demonstration in animals that larger amounts of it and pyridoxine are necessary in hyperthyroidism.¹⁸

The use of pantothenic acid to restore color of graying hair is well known. Results are equivocal. Para-aminobenzoic acid, considered a part of the B complex, has also been used.^{71a,b} It is known to modify melanin formation. A darkening of the hair is reported in 3 to 8 weeks with oral doses of 100 mg. twice daily. The use of these preparations is still in the experimental stage.

Biotin. So-called vitamin H, or biotin, is the curative factor for egg white injury in rats and has been considered a part of the B complex. Sydenstricker and his associates⁸³ placed a group of volunteers on a diet low in biotin and high in avidin, a substance which makes biotin unavailable for the organism. Definite findings were observed. In 3 to 4 weeks, a scaly desquamation appeared and lasted 7 to 10 days. In

the seventh to eighth week, a grayish pallor of the skin and mucous membranes developed. The color was out of proportion to the blood picture. Lassitude, depression, muscular pains and paresthesias, somnolence, precordial distress, and, in 2 instances, a mild panic state were observed. Biotin in 3 daily doses totaling 150 to 300 mg. controlled the symptoms in 3 to 5 days.

Vitamin C. This vitamin is one in which determinations of blood levels has become a part of clinical laboratory diagnosis. Study of induced deficiency has shown that a reevaluation of the interpretation of vitamin C blood levels is necessary.⁹⁶ Levels previously considered indicative of scurvy, below 0.4 mg. per 100 cc. of plasma, may be found in normal individuals. Determinations on the white cell-platelet fraction and on whole blood are more reliable than determinations on plasma. High values indicate the presence of body reserves. Low values, even approaching zero, have developed in persons with 75% reserves as well as in those with scurvy. It is here that saturation tests may be of help in diagnosis.

The increased requirements for vitamin C in diseases which increase metabolic processes is evident. This occurs in such conditions as hyperthyroidism, tuberculosis, rheumatic fever, pregnancy, pneumonia, osteomyelitis, and other febrile states. In inadequate intake, or increased loss, as in diarrheas, the requirements are also evident. In addition, the use of vitamin C has been advocated in many diseases where clear-cut indications are not evident, and in most such conditions the results with its use are doubtful. Such conditions include senescence, certain types of cutaneous pigmentation, essential hematuria and chronic lead poisoning. Arsenical reactions complicating the treatment of syphilis, radiation sickness, gingivitis, corneal inflammation, fall into the same group. In all these, vitamin C has been reported as beneficial in treatment, but its importance is still not established. In anemia, thought to result from vitamin C deficiency, iron has been shown to be effective when vitamin C is not.⁴¹ Deficiency associated with gastric lesions has been described.⁴⁴

Vitamin D. Evidence has long indicated that rickets may be due to more than vitamin D deficiency, and may include endocrine and general nutritional factors. In certain cases of low phosphorus rickets, which are refractory to treatment with vitamin D and have associated renal lesions, it is possible²⁹ that the development of the rickets is due to a failure of the renal tubular mechanisms concerned with the reabsorption of phosphate. Animal studies⁵¹ suggest that renal damage may be important in the production of evidence of toxicity from excessive dosage of vitamin D.

So-called massive dose therapy, both orally and parenterally,^{85a,b} has been utilized in the treatment and prophylaxis of rickets. Curative doses of vitamin D₂ or D₃, representing 600,000 I.U. or more, have not been accompanied by evidences of toxicity. Single prophylactic doses of 400,000 to 500,000 I.U. parenterally have been given for protection for the entire winter period. Such treatment is not generally used. Several autopsies are on record^{85c} of patients who had received over a million units 3 to 26 days before death. No changes indicative of hypervitaminosis D were found. While hypervitaminosis D has been produced, the use of vitamins D₂ and D₃ has not resulted in toxic

symptoms in over 600 cases. Irradiation of vitamin D preparations is thought to result also in the production of other irradiation products than vitamin D₂, which probably produce toxic symptoms. Vollmer states that the fish liver oils do not contain these toxic products. No permanent damage has been noted in the treatment of arthritis with doses of 200,000 to 1,000,000 units over periods of weeks. However, such symptoms as nausea, frequency of urination, lassitude, diarrhea, pains, anorexia and vomiting do occur.

Reports of the treatment of psoriasis and rheumatoid arthritis with vitamin D are still conflicting.^{72,77} Freyberg²⁵ has pointed out that there is no good evidence for the existence of any antirheumatic vitamin.

Vitamin E. The importance of vitamin E in human nutrition is not yet established. Until recently its use was confined to the treatment of habitual abortions and functional sterility, and success is claimed in 75% to 80% of the cases.⁸ Other forms of treatment have given equally good figures so that the value of vitamin E remains to be established. The Council on Pharmacy and Chemistry of the American Medical Association⁶⁰ has not accepted the claims in the treatment of habitual abortion.

The production of paralysis and muscular lesions in experimental animals with vitamin E deficiency has led to the widespread use of this substance in the treatment of a variety of nervous and muscular disorders, both with wheat germ oil and synthetic preparations. Muscular dystrophies and atrophies, amyotrophic lateral sclerosis, Parkinsonism and other neurologic disorders have been included. Claims of success and failure have appeared with vitamin E used alone and in conjunction with other vitamin products, especially the B group.⁸⁰ Lubin⁴³ applied quantitative methods to this problem. Thirty-five patients were treated with large doses of alpha-tocopherol and most were followed at intervals by dynamometric and electrical methods for muscular strength, and measurements of the creatinine and creatine output. In 31 patients, the condition remained stationary or became worse during the period of medication. In the 4 remaining patients, improvement was considered unrelated to the intake of tocopherol.

Vitamin E is said to benefit primary but not secondary fibrositis.^{32,78}

Vitamin K. A great number of compounds have been found which have the activity of vitamin K. Of these, 2-methyl-1, 4-naphthoquinone is the most widely used synthetic and has been given the name "menadiione." The success of this, and other preparations having the activity of vitamin K, in the correction of the low blood prothrombin levels resulting from vitamin K deficiency is without question. When low prothrombin levels in the body are sufficient to interfere with the clotting mechanism, hemorrhage results. Probably the best known example of the disturbance in this mechanism is obstructive jaundice in which the lack of bile in the gastro-intestinal tract interferes with proper absorption of vitamin K. Deficiency may occur because of inadequate diet, and in diarrhea, as in sprue, celiac disease and ulcerative colitis. Primary hepatic injury may interfere with the metabolism of vitamin K and prothrombin even when the vitamin is well absorbed. This fact has formed the basis for a liver function test utilizing vitamin K and its effect on blood prothrombin levels, for vitamin K therapy has no effect in elevating low blood prothrombin levels resulting from severe

hepatic injury. Hypoprothrombinemia occurs frequently in pulmonary tuberculosis. Low values have been reported with pulmonary hemorrhage⁴⁰ and vitamin K preparations have been suggested as useful in the control of such hemorrhage. Hypoprothrombinemia also occurs in pernicious anemia in relapse, usually in levels between 40% and 65% of normal. Vitamin K therapy is reported as unsuccessful in correcting this change⁸⁸ while there is a rise with specific liver therapy.

In the newborn, the prothrombin time is often prolonged, particularly from the second to the fifth day. This change is upon the basis of vitamin K deficiency and, if sufficiently marked, hemorrhagic disease of the newborn appears. This change is not related to the mother's diet, but prothrombin levels below those usually seen at this time may develop if sodium pentobarbital has been used as an analgesic in the mother.²³

Despite the fact that an adequate diet in the mother does not protect the child, administration of vitamin K before delivery does. Beck, Taylor and Colburn⁵ found only 5 (0.5%) of 1022 infants of mothers so treated with evidences of hemorrhage, while 21 (2%) of 1037 controls showed such evidences. This represents a reduction of 75% with treatment. In this study menadione was used in 2 mg. doses at the time of admission to the hospital for delivery and the dose was repeated at 6-hour intervals throughout labor.

How late in labor menadione administered to the mother may be effective in the newborn is an important question. Hellman, Shettles and Eastman³⁰ found definite elevations in prothrombin levels in the infant when vitamin K was given as late as 4 hours before delivery. In general, better results are obtained by administration of the vitamin to the mother than to the child after birth, even though the daily requirement of the newborn has been estimated as low as 1 μ g. of the synthetic vitamin. In a study⁶⁵ in which these factors were analyzed, 711 of 1693 newborn infants were given vitamin K in the first 10 days of life. As soon as they reached the nursery, a 1 mg. tablet was dissolved in a teaspoon of water and given with a medicine dropper. If regurgitated, the dose was repeated. In 606 instances, the prothrombin determinations on cord blood were similar to those on the mother's plasma. The values diminished in the first 3 days and rose in the next 3, almost to reach the cord level by the seventh day. Levels did not rise above those of the cord, whereas values above these were obtained by administration of the vitamin to the mother before delivery. These authors found the frequency of conjunctival, vaginal, petechial, cerebral, and umbilical hemorrhage unchanged by vitamin K therapy.

Intravenous use of menadione and other compounds, such as tetra sodium salt of 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester,¹⁶ and 4-amino-2-methyl-1-naphthol hydrochloride eliminates bile salt administration and responses in the prothrombin time have occurred in 1 to 3 hours.¹

The extensive use of purified synthetic preparations, especially those given parenterally, suggests the possibility of toxicity and hypervitaminosis from overdosage. In animals⁶⁹ large doses have produced respiratory depression and congestion of organs. The usual dosage in man has produced no untoward symptoms. Methyl-naphthoquinone,

1% in an ointment base, has produced dermatitis in 5 of 9 patients so treated.⁵³

It is of interest to note that the prolongation of the prothrombin time resulting from the administration of dicoumarin is not corrected by menadione in 10 mg. doses.⁴⁸

Vitamin P. A second hemorrhagic factor is known to be associated with vitamin C in citrus fruits. This compound is a flavone. Its use in both animals and man in controlling purpuras associated with low capillary resistance is reported as successful.^{37,58,67} While the deficiency may occur along with vitamin C deficiency, it is unrelated in its development to vitamin C metabolism. Increases in capillary fragility in purpura associated with allergic states, infection, arsenic poisoning and psoriasis have responded to oral doses in the range of 100 to 150 mg. daily.

WILLIAM A. SODEMAN, M.D.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.

PROFESSOR OF PSYCHIATRY, SCHOOL OF MEDICINE, UNIVERSITY OF COLORADO;
DIRECTOR, COLORADO PSYCHOPATHIC HOSPITAL, DENVER, COLO.

AND

GEORGE S. JOHNSON, M.D.

PROFESSOR OF PSYCHIATRY, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

THE progress article in this Department will appear in the February number.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 17, 1942

Measurements of Uterine Contractions of 105 Patients Throughout Labor. DOUGLAS P. MURPHY (Department of Obstetrics and Gynecology, University of Pennsylvania). Uterine motility was recorded with a Lorand tocograph at intervals of 1 to 2 hours from the time that the patient entered the hospital in labor until delivery took place. The Lorand tocograph is a simply constructed mechanical device which registers the uterine movements through the medium of the anterior abdominal wall. It supplies a graphic record of this activity.

Tabulated measurements of the graphs indicated the changes in magnitude which the uterine tonus, strength, duration and frequency of the intermittent contractions undergo as labor advances, and also in what degree parity and feto-pelvic disproportion modify this activity.

The Determination of Sodium in the Glomerular Fluid of Necturi. PHYLLIS A. BOTT (Laboratory of Pharmacology, University of Pennsylvania, and Department of Physiological Chemistry, Woman's Medical College of Pennsylvania). The sodium content of glomerular fluid was compared with that of serum in a series of glomerular puncture experiments on Necturi. For use in these and other studies on glomerular and tubular fluid an ultramicro method determining as little as 0.3 microgram of sodium has been developed. The steps involved in the method are as follows: 1, precipitation of sodium as sodium zinc uranium acetate in capillary tubes; 2, washing the precipitate on special micro filters with a solution of magnesium uranium acetate saturated with sodium magnesium uranium acetate, followed by alcohol and ether; and, 3, photoelectric determination of zinc (in the Evelyn macrocolorimeter) in an aqueous solution of the dissolved precipitate by

means of the red color produced with alkaline diphenylthiocarbazone. For determination of sodium in serum the proteins are first precipitated in capillary tubes with 20% triehloracetic acid.

The sodium content of glomerular fluid was found to be within 5% of that in serum in 9 out of 15 experiments. The greatest differences were -14% and +9%. This is regarded as additional evidence that the glomerular fluid is an ultrafiltrate of plasma.

Some Effects of Tannic Acid on the Cell Surface. M. H. JACOBS, DOROTHY R. STEWART and MARY K. BUTLER (Department of Physiology, University of Pennsylvania). Tannic acid is known to produce certain characteristic effects on molecular films of proteins, one of the most striking being the enormous decrease in permeability to ions indicated by the rise in electrical resistance and electrical capacity produced by "tanning." (Dean, Cole and Curtis: *Science*, 91, 50, 1940). The normal permeability of the erythrocyte to certain anions can be shown to be greatly decreased by tannic acid under conditions that leave its permeability to water, fatty acids, NH_3 , thiourea, glycerol, ethylene glycol, diethylene glycol, triethylene glycol and other undissociated molecules little affected. Thus the osmotic shrinkage that occurs when Cl^- ions from the cell are exchanged for HCO_3^- or SO_4^{--} ions from outside is strongly retarded by concentrations of tannic acid sufficiently low to cause no agglutination of the cells and to have little effect on their permeability to many undissociated molecules. This effect can be more or less completely reversed by adding a small quantity of gelatin to a suspension of the "tanned" cells or by washing them with gelatin-containing saline. Tannic acid has little effect on the rate of hemolysis in solutions of ammonium acetate, which can enter erythrocytes by a purely molecular mechanism; but in solutions of NH_4Cl , in which an ionic exchange is involved, the retardation may be very great. In the case of NH_4Cl "catalyzed" by NH_4HCO_3 the initial swelling, believed to be associated with the entrance of NH_3 and CO_2 (Jacobs: Cold Spring Harbor *Symposia*, 8, 30, 1940) is unchecked by tannic acid, but the later ionic exchange of HCO_3^- for Cl^- seems to be greatly slowed. Likewise, the peculiar volume changes produced by NH_4OH are affected by tannic acid as they should be if there were an initial rapid entrance of NH_3 , followed by a later ionic exchange.

Studies on the Distribution of Potential of Ventricular Origin. CHARLES C. WOLFERTH, MARY M. LIVEZEY and FRANCIS C. WOOD (Robinette Foundation, University of Pennsylvania). It has been shown in a previous study that the two patterns of potential variation found on the chest just external to the right and left borders of the heart remain relatively intact along lines to the corresponding shoulder tips, except for decrement as distance from the heart increases. These relationships made possible development of the procedure which we have previously called "the method of balanced potentials." By the use of this method each of these patterns can be practically eliminated from an electrocardiogram, except insofar as it may be transmitted to

the exploring electrode. Further studies by the method of balanced potentials show that there are but three patterns of potential variation with widespread distribution on the body surface. These are the two mentioned above and a pattern found below the diaphragm. On the precordium, however, there is almost infinite variation in pattern which can be demonstrated by slight shifts in position of the exploring electrode. These precordial patterns are distributed to the surface of the upper abdomen with marked decrement as distance from the heart increases.

In animal experiments using needle electrodes insulated except at the tip, it was found that in regions not more than 2 inches from some part of the external surface of the ventricles (precordium, lungs, diaphragm) slight change in position of the exploring electrode resulted in change in the pattern of potential variation. Reduction in magnitude of potential variation was rapid as distance from the heart increased. However, on peripheral areas of the diaphragm, abdominal organs, abdominal wall and hind legs, the pattern remained practically constant and only slight decrement was noted as distance from the heart increased.

On the basis of these findings it is concluded that certain modifications in the technique of clinical electrocardiography are desirable. The method of balanced potentials is too time-consuming for routine use. However, practically the same results can be obtained by pairing the exploring electrode with one placed over an area of slight potential variation, such as the right scapular region. Tracings should be made with the exploring electrode on the C_1 to C_6 positions inclusive and on some position at least several inches below the diaphragm. (The most favorable position will have to be determined by further study.) In certain cases it is possible that additional information may be obtained by placing the exploring electrode in the esophagus below the auricular level. The three conventional limb leads of Einthoven are not recommended. They are not merely superfluous but may be misleading.

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RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal* of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the more exact meaning.

THE EDITOR.

THE
AMERICAN JOURNAL
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FEBRUARY, 1943

ORIGINAL ARTICLES

TISSUE CULTURE STUDIES ON CYTOTOXICITY OF BACTERI-
CIDAL AGENTS

I. EFFECTS OF GRAMICIDIN, TYROCIDINE AND PENICILLIN ON
CULTURES OF MAMMALIAN LYMPH NODE

By WALLACE E. HERRELL, M.D.

DIVISION OF MEDICINE, MAYO CLINIC

AND

DOROTHY HEILMAN, M.D.

DIVISION OF EXPERIMENTAL MEDICINE, MAYO FOUNDATION
ROCHESTER, MINN.

SOME of the biologic properties of gramicidin and tyrocidine have been studied with special emphasis on the activity of these agents in the presence of serum plasma, tissue extract and growing tissue. A tissue culture medium has been used in order to provide some of the constituents found *in vivo* and in whose presence a drug must act in order to be effective. Reports have been made on the bactericidal activity of gramicidin, tyrocidine and penicillin for Gram-positive organisms growing in the tissue culture medium.^{4,6} Studies on the hemolytic effect of gramicidin and tyrocidine on erythrocytes suspended in the tissue culture medium have also been reported.^{3,4} Gramicidin was found to be more hemolytic than tyrocidine as well as more bactericidal under these conditions. Penicillin did not cause hemolysis although its bactericidal activity was as great as that of gramicidin.

The present report deals with the effect of gramicidin, tyrocidine and penicillin on the migration of lymphocytes and other cells in cultures of the mesenteric lymph node of the rabbit.

Methods. The technique used was similar to the modified Maximow type of preparation described by King and Henschel.⁹

Young adult male rabbits were used exclusively and the plasma, serum and tissues used in each series of cultures were obtained from the same animal. Blood was obtained by carotid cannulation of the rabbit with the animal under light ether anesthesia. The solution of heparin used in the preparation of plasma contained 0.04% of purified heparin (Connaught Laboratories) and 0.8% sodium chloride. This solution was sterilized by Berkefeld filtration and approximately 0.25 cc. was used for 15 cc. of blood. A serum extract was prepared by extracting chick embryos of 8 days of incubation with rabbit's serum in the proportion of 1 embryo to 5 cc. of serum.

Tissue from the mesenteric lymph node of the rabbit was removed and fragmented under sterile conditions immediately after death of the animal. Suitable explants of a similar size, 1.5 to 2.5 mm. in diameter, were placed in 3 series of 12 fragments each. Care was taken to match fragments of a similar size and shape so that the resulting groups were as nearly alike as possible. Cultures of explants in the control series did not receive any bactericidal agent, whereas gramicidin was added to cultures of the second series and tyrocidine to cultures of the third series.

Similar experiments were carried out with penicillin and consisted of 2 series of 12 explants each. Tyrode's solution was added to the control series and a suitable dilution of penicillin in Tyrode's solution was added to the second series.

Suspensions of the bactericidal agent to be tested in an amount equal to 10% of the volume of the final tissue culture clot were added to the serum extract before the cultures were made. The purified gramicidin used was prepared by Osterberg according to the method of Hotchkiss and Dubos⁷ from crude tyrothricin. Sharp & Dohme kindly furnished the crude tyrothricin as well as the purified tyrocidine used in this study. Stock solutions of gramicidin and tyrocidine in 95% alcohol were prepared containing 20 mg. per cc. Dilutions of the stock solution were made in Tyrode's solution just before use. Similar dilutions of 95% alcohol in Tyrode's solution were added to the control series of cultures.

Two samples of penicillin were used in this study. One sample, obtained through the courtesy of Dr. Florey and Dr. Heatley, contained pyrogens and had a potency of 42 Oxford units per mg. This sample was used in the group of experiments in which 0.2% of penicillin was tested. The second sample, obtained from Merck & Co., and having a potency about two-thirds that of the first sample, was used in experiments in which larger amounts of the drug were tested. Solutions of penicillin in Tyrode's solution were preserved in solid carbon dioxide.

The individual tissue cultures were made as follows: Each explant was placed on a 22 mm. round coverslip in a clot consisting of 1 drop of plasma and 3 drops of serum-chick-embryo extract. The cover-

slip was secured to a heavier glass slide by means of a drop of saline solution and the preparation was covered by a hollow glass slide rimmed with petrolatum, then sealed with a mixture of paraffin and petrolatum. Cultures were incubated as lying drops at 37.5° C. for 24 hours. Determinations of the extent of migration of cells were made according to the method described by Stenstrom, King and Henschel.¹⁰ With the use of an ocular micrometer at a magnification of 60 times, a measurement was made of the radius of the widest part of the migration zone from the edge of the fragment to the outer limit of migrating cells (135 ocular micrometer units are equal to 1 mm.). The average value in ocular micrometer units was determined for each series of 12 cultures. From a statistical study of cultures of normal lymph node in which each experiment consisted of 2 matched groups of 12 fragments each, it was found that the error in such a system would not be expected to exceed 20.8 units.

TABLE 1.—EFFECT OF GRAMICIDIN AND TYROCIDINE ON MIGRATION OF LYMPHOCYTES

Average migration, controls, ocular units*	Average migration, cultures containing gramicidin, ocular units* 5 µg. per cc.	Variation from controls, %	Average migration, cultures containing tyrocidine, ocular units* 5 µg. per cc.	Variation from controls, %
251	236	-6	233	-7
142	138	-3	150	+6
232	225	-3	227	-2
177	184	+4	187	+6
256	267	+4	272	+6
20 µg. per cc.				
204	178	-13	198	-3
147	153	+4	156	+6
300	303	-1	317	+6
197	197	0	199	+1
225	217	-4	244	+8
264	264	0	246	-7
218	206	-6	200	-8
80 µg. per cc.				
199†	160	-20	207	+4
236	197	-17	217	-8
276	236	-14	267	-3
260	201	-23	230	-12
229	190	-17	225	-2
207	176	-15	220	+6
100 µg. per cc.				
147	111	-24	139	-5
239	187	-22	229	-4
296	234	-21	235	-4
227	172	-24	226	0
202	159	-21	207	+2

* 135 ocular units = 1 mm.

† This test was done with purified gramicidin and tyrocidine obtained from Dubos and Hotchkiss.

Values in italics show significant variation from controls.

After measurements had been made, the cultures were fixed in Zenkerformol fixative and sections were made according to a method described by King⁸ and were stained by the Dominici technique.

Results. Cultures containing small amounts of gramicidin and tyrocidine (5 μ g. and 20 μ g. per cc.) did not show a significant alteration in migration when compared with control cultures (Table 1). Examination of the stained sections of cultures containing gramicidin and tyrocidine showed little difference in the morphologic characteristics of the migrating cells as compared with controls. In a few instances in experiments in which 20 μ g. per cc. of gramicidin were used there were fewer intact erythrocytes in the original tissue fragment. This was due to the hemolytic effect of gramicidin.

Gramicidin in a concentration of 80 μ g. per cc. or more caused a significant decrease in the extent of migration of lymphocytes in all tests, whereas the same amounts of tyrocidine caused a significant decrease in migration in only 1 out of 11 tests. Histologic examination showed a greater degree of degeneration of lymphocytic elements in cultures containing gramicidin than in cultures of the control series. There was an increased amount of fragmentation of the nuclei of lymphocytes and granulocytes which had undergone pyknosis. In many instances the granules of the pseudo-eosinophils were distinct in spite of nuclear degeneration. Larger ameboid cells that were still intact showed a distortion of cell outlines and vacuolization of the cytoplasm. Nuclear material in these cells appeared to be less prominent than in similar cells of control cultures. No intact erythrocytes were seen in the explants; however, there was much erythrocyte debris. Examination of stained preparations containing tyrocidine showed that they did not differ markedly from control cultures. Intact erythrocytes were observed in the explants and the number of surviving granulocytes in the migration zones was actually somewhat larger than in control cultures. The lymphocytic elements appeared normal for this stage of growth.

It was not possible to make satisfactory measurements on cultures containing more than 100 μ g. per cc. of gramicidin or tyrocidine because the insoluble particles of both substances obscured the cells in the migration zone. Another type of preparation has been used in another series of experiments in order to explore more fully the relative toxicity of the various products of the soil bacillus.* It was possible, however, to incorporate relatively large amounts of penicillin into the tissue culture medium because of its solubility. It was necessary to use large amounts of penicillin in order to cause any demonstrable cytotoxicity (Table 2). Only when 1 mg. per cc. or more was used was there any significant decrease in migration. Thus, 10 times as much penicillin as gramicidin may be used before the same degree of inhibition of migration results. Histologic examination of cultures containing 1 mg. per cc. of penicillin showed that

* To be reported.

fewer ameboid lymphocytes were present and there was an increased amount of degeneration of the granulocytes. The larger phagocytic cells were rounded up and showed varying degrees of cellular disintegration. These degenerative changes are the same as those observed with a number of other toxic agents and are more or less nonspecific in character. No change was observed in erythrocytes present in the explants treated with penicillin.

TABLE 2.—EFFECT OF PENICILLIN ON MIGRATION OF LYMPHOCYTES

Average migration, controls, ocular units*	Average migration, cultures containing penicillin, ocular units*	Variation from controls, %
	200 μ g. per cc.	
258	256	-1
202	219	+8
219	225	+3
219	207	-5
199	188	-6
	500 μ g. per cc.	
228	223	-2
	1000 μ g. per cc.	
276	200	-28
	2000 μ g. per cc.	
210	103	-51

* 135 ocular units = 1 mm.

Italic values show significant variation from controls.

Comment. Although gramicidin and tyrocidine are lethal for laboratory animals when given intravenously, clinical experience with the local use of these products would indicate that their toxicity for tissues is small.⁴ From this study it appears that gramicidin is more toxic than tyrocidine; however, there is a wide range between the amount of gramicidin that would cause tissue damage and the amount effective against most Gram-positive cocci found in infected wounds. Henle and Zittle⁵ reported that gramicidin was more active than tyrocidine in decreasing the respiration and motility of bovine spermatozoa. This agrees with our results. It appears from available data that gramicidin is more toxic for mammalian tissues than tyrocidine as well as more bactericidal for Gram-positive bacteria and more destructive for erythrocytes.

The results of this study also shed some light on the question whether or not tyrothricin should be fractionated for clinical use. Since gramicidin is more cytotoxic than tyrocidine, there would be little advantage in using purified gramicidin for the purpose of avoiding toxicity. Tyrocidine aids in keeping gramicidin in suspension and also inhibits Gram-negative bacteria on which gramicidin is said to have little effect. However, research now in progress indicates that there may be other reasons for using purified gramicidin under certain conditions.

The remarkably low tissue toxicity of penicillin has already been well demonstrated in the work of Fleming² and of Florey¹ and his coworkers. Our results confirm their observations.

Conclusions. Gramicidin is more toxic than tyrocidine for cells migrating from explants of mammalian lymph node. However, the amount of gramicidin necessary to produce a toxic effect was large compared with the amounts necessary to kill most Gram-positive cocci.

Penicillin is approximately one-tenth as toxic by weight as gramicidin when studied in the same preparation containing explants of lymph nodes.

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ORNITHOSIS (PSITTACOSIS)

A REPORT OF 3 CASES, AND A HISTORICAL, CLINICAL, AND LABORATORY COMPARISON WITH HUMAN ATYPICAL (VIRUS) PNEUMONIA

By CUTTING B. FAVOUR, M.D.

RESIDENT PHYSICIAN. PETER BENT BRIGHAM HOSPITAL
BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School)

It has been customary to divide acute pneumonitis into lobar and bronchopneumonia. Lobar pneumonia is usually associated with the lower numbered types of pneumococci; whereas bronchopneumonia is due to various microorganisms, either by primary bacterial invasion or secondary to operations, chronic disease, or acute systemic infection, such as measles, influenza or tular-
emia.^{22,23,38,45}

In the past few years, however, attention has been directed to a new form of bronchopneumonia not accompanied by secondary bacterial infection. It is believed that this pneumonia is due to a virus and it has variously been called atypical bronchopneumonia, virus pneumonia, pneumonia variety X, and so forth.^{1,8,13,18,19,23,25.}

33,36,37,47,53,51,59,67 Much confusion has arisen over its etiology, clinical picture, and the pathologic process going on in the lungs. In the last year our attention has been called to this confusion because of the number of these cases on the wards of this hospital. Three cases, 1 mild, 1 severe, and 1 very severe we have been able to identify as probable ornithosis (psittacosis) by the complement-fixation test. Other cases running parallel clinical courses, but not due to the virus of ornithosis, suggested close similarities between ornithosis and atypical pneumonia. A brief review of the literature substantiates this finding. It is a presentation of these likenesses which forms the basis of this report.

History of Ornithosis. As early as 1879, Ritter⁵⁶ in Switzerland described 7 cases of an unusual pneumonia (with the postmortem findings on 1) which occurred after contact with tropical birds. The illness was characterized clinically by a typhoid-like course with an unusual bronchopneumonia. On pathologic examination, the pulmonary alveoli seemed to be filled with desquamating respiratory epithelium. Sporadic cases continued to be seen in Europe, but not until 1892 did the disease assume clinical importance. In that year two bird importers, Marion and Dubois, started from Buenos Aires with 500 parrots.³⁶ En route 310 died, each importer arriving in Paris with 95 birds. Marion went to live with his brother, and shortly thereafter both developed a pneumonia from which the brother died. Dubois likewise developed pneumonia and recovered, but 7 members of his landlord's family died of pneumonia and numerous neighbors were infected. Dujardin-Beaumetz¹⁶ was assigned to study the new disease and arrived at the conclusion that it was a grippal infectious pneumonia. Nocard⁴⁸ isolated from the bone marrow of a dead parrot a bacillus of the enteric group, which he considered the causative agent. Not until another epidemic in Paris in 1894 did the disease receive a specific name. Morange⁴⁶ established the parrot as a vector and called the disease "psittacosis" after the Greek *ψιττακός* ("psittakos"), a parrot.

Psittacosis has occurred sporadically in other countries. Cases were reported in Italy in 1895,⁴² in the United States in 1887⁹ and 1904,⁶⁶ in England in 1892,⁷⁰ and in Germany in 1909.⁴ In 1920 the concept of its bacterial etiology was revived by Perry,⁴⁹ who found *Bacillus aertrycke* in healthy parrots. This organism was culturally and serologically the same as Nocard's bacillus. In general, however, no definite etiology was known and the disease was regarded as rare.

Epidemic of 1929. During the summer of 1929 an epidemic of atypical pneumonia broke out in Cordoba, Argentina.⁶ Cordoba is the scene of an annual fair where bird dealers congregate to buy parrots imported from Brazil and Paraguay. In 1929 there were many sick and dying birds in the displays visited by the town folk. So many townsmen became ill that the dealers with their birds

moved to nearby Tucuman. Again the pneumonia followed, and the dealers moved on, causing still other epidemics. Eventually many of these birds found their way to Europe and to this country. The clinical features of the Argentine epidemic were those which had previously marked this illness: headache, lassitude, a rapidly rising temperature, vomiting, delirium, intense thirst, a relatively slow pulse, a non-palpable spleen and variable forms of pneumonia associated with a dry spasmodic cough. When the epidemic came to England, Thompson reported the first 4 cases,^{64a,b} and in 1930 outlined the first modern clinical picture of the disease.^{64c} With current laboratory techniques Bedson, Western, and Simpson^{7a,b} were able to isolate a filterable virus both from sick parrots and from patients. This virus was infectious for hens, parrots, and budgarigars, but not for pigeons or guinea pigs.

Following the shipment of several large orders of parrots to New York pet dealers, human infections began to appear in this country.³ During the winter of 1929-30, 169 cases with 33 deaths (19% mortality) were reported. The U. S. Public Health Service found 74 foci in 15 states, 16 additional laboratory infections with 2 deaths, and 12 further cases on ships carrying parrots. In 55 foci parrots were vectors, and parrakeets, love-birds, canaries, and a variety of psittacine birds in the others. Infected birds had been imported from Brazil, Colombia, Cuba, Nicaragua, Honduras, Trinidad, Salvador, Mexico, Germany, and Japan. In addition, psittacosis was reported in Argentina, Algeria, Germany, Austria, Holland, Czechoslovakia, Denmark, Switzerland, France, Spain, Portugal, Canada, and the Hawaiian Islands. Some idea of the size of the bird industry at this time can be gained by the importation figures for 1929. In that year about 50,000 birds of the parrot family and about 350,000 canaries were brought into the United States.

Psittacosis Control. The relatively high mortality attracted great publicity, and in January 1930, an embargo by executive order was placed on the importation of parrots.²⁹ In 1932 shell parrakeets, Amazons, love-birds, Mexican doubleheads, African grays, cockatoos, macaws, lorries, and all similar birds were added to the embargo. Despite these measures, psittacosis became endemic in the aviaries of California, and new infections continued to occur after contact with acute or latent infections in these home-grown birds. In 1933 Meyer found as many as 60% of the birds in some breeding lofts to be infected.^{43a} By rigid restrictions on interstate shipments from the breeding aviaries, the epidemic was gradually controlled. During 1932 there were 75 cases with 7 deaths; in 1933, 15 cases with 4 deaths; and in 1934 one localized epidemic in a Pittsburgh department store, following the arrival of a shipment of infected parrots and parrakeets, causing 35 cases and 10 deaths.⁵ Since that time only sporadic cases have been reported.

Psittacosis Since 1932. Meyer and his group took up the study of the ecology of psittacosis and found that human infections could be traced to canaries as well as to psittacine species.⁴⁴ Ruys reported finches as the source of human cases,⁵⁸ and Haagen and Mauer²⁷ implicated the arctic fulmar, a sea bird, as a reservoir for human ornithosis. Five orders and multiple species, including the chicken, dove, and many types of finch, are now known to be infected.^{43a,b} More recently, domestic pigeons have been found to harbor the virus as a latent infection^{43b,50} In addition, the National Zoo in Washington has reported psittacosis in its birds.⁶⁵ It is because of these multiple hosts that Meyer^{43b} has suggested "ornithotic" pneumonia as a more appropriate term.

Ornithotic Infection Chains. From the studies of Meyer^{43,44} and Burnet,^{11,12} it appears that the virulence of the different psittacosis strains is related to the duration and stability of the host-parasite relationship. In Australia, the main theater of parrot evolution, this relation has reached a highly developed stage of "symbiosis." The virus is easily transmitted to new generations of birds, usually while they are young; it maintains itself most often as a latent infection, and there is a low degree of virulence for heterogeneous hosts. For this reason it is only after numerous passages that the Australian strains can be made mouse-virulent, whereas European and American psittacosis are readily transmitted to mice. The clinical expression of this phenomenon is the rarity of human cases of psittacosis in Australia compared with its relative frequency in America and Europe.

There is also a wide variation in host susceptibility. In the Java rice bird, once infection is established, the mortality is 95%, while the infected fulmar or parrot may readily survive and become a healthy carrier. Rice bird droppings are relatively non-infectious. Those of the fulmar, parrakeet, or parrot, contain the virus in large amounts, and may be responsible for respiratory or enteric invasion in birds and for respiratory invasion in man. This is of practical importance in collecting epidemiologic data. When canaries, finches, and hens are suspected, the contact is direct, as in handling infected birds. When psittacine birds, fulmars and pigeons, are involved, the contact is usually by dust.

Age and environment are additional factors in ornithosis infection chains. Children and adult birds are more resistant to the disease. Crowding and exposure will activate latent infections and start new epidemics. The U. S. Public Health Service first noticed that a change of weather or a change of locality precipitated active psittacosis infection in birds carrying the disease.²⁹ Burnet and MacNamara¹² found that crowding, poor lighting, and poor food activated latent psittacosis in cockatoos recently brought from the bush. Meyer^{43a} produced 100% mortality in a group of infected parrakeets by simulating the conditions of a pet shop. Whether

this is analogous to the greater incidence of human atypical pneumonia in cold weather and in institutional groups invites speculation.

Bronchopneumonias Other Than Ornithosis and Atypical Pneumonia. To W. G. MacCallum³⁸ we owe credit for the rebirth of the concept of interstitial bronchopneumonia. Working on the war pneumonias in 1918, he was the first to differentiate between the underlying interstitial bronchopneumonia of influenza and the changes wrought by secondary bacterial invaders. At that time the influenzal type of pneumonia was thought to be a new disease. This notion MacCallum brilliantly refuted. By historical data, as well as by actual section made from Civil War specimens preserved in the Army Medical Museum, he brought evidence that these bacterial-invaded epidemic pneumonias were as ancient as wars themselves. Similar epidemics could be traced as far back as there were adequate clinical records available. The most interesting part of his work to us now is the clear-cut demonstration of an interstitial bronchopneumonia, sometimes only very little overrun with secondary bacterial invaders, and yet in itself fatal. These MacCallum observed in conjunction with pertussis, measles, and a variety of upper respiratory tract infections, and even as a primary disease. Where bacteria were not present in the tissues, the pathologic changes were not unlike those seen in modern atypical pneumonia. Bronchiolitis, areas of patchy atelectasis or ischemic infarcts, hemorrhage into the tissues, dense mononuclear exudate on and infiltrating through the bronchial surfaces, desquamating alveolar epithelium and thickened alveolar septa characterized the process. We now know that this type of pneumonia can be caused by the influenza virus.⁴¹ Recently Finland and his co-workers,²² and Michael⁴⁵ have showed that the massive invasion of staphylococcic pneumonia may be secondary to an influenza virus infection.

That other bronchopneumonias are due to the combined action of a virus and bacteria was suggested by McCordock,⁴⁰ who found intranuclear inclusions in one-third of a series of autopsies on cases of pertussis bronchopneumonia. Rich⁵⁵ also found inclusion bodies in the kidneys of such cases. Subsequently, by intratracheal inoculation in animals, McCordock and Muckenfuss⁴¹ produced a similar pathologic picture, whether bacteria and vaccinia virus together or the virus alone were used. That much the same situation may occur in measles is suggested by Kohn and Koiransky,³⁴ who found definite changes in routine chest plates taken in 130 cases of ordinary uncomplicated measles.

Other Interstitial Pneumonias. More support is added to the virus origin of many of these pneumonias in the report by Waring, Neuburger, and Gcever⁶⁸ of 2 cases, 1 fatal, of uncomplicated chickenpox bronchopneumonia. We may not be able to implicate a virus always, however, for so-called "rheumatic" pneumonia^{24,65}

may show proliferation of the alveolar lining cells, a mononuclear alveolar exudate, vascular damage, and destruction of the small bronchi. Similarly, excessive radiation of the lungs⁶⁹ both in animals and man may give rise to a form of interstitial pneumonitis.

The "New" Disease. During the last 10 years a number of institutional outbreaks of atypical pneumonia have attracted attention. In 1932 Bowen⁸ observed 89 cases of a peculiar atypical pneumonia occurring in the white troops in Hawaii. The illness was influenza-like, physical signs were minimal, and roentgenograms revealed a spotty pneumonia extending into the lower lobes. Since that time there has been a flood of clinical reports on a similar form of pneumonia, also showing a typhoid-like chart, and disproportionately few physical signs for the pneumonia so evident by roentgenogram. Epidemiologic study suggests that it is an air-borne infection, that infectiousness is high, and that clinical variations are numerous. It occurs most often in the fall and early winter in close-knit or crowded populations. Fatigue, poor living habits, or underlying chronic disease are predisposing factors. In young adults it is a mild disease of relatively short duration, while in the older age groups the course is long and there are occasional fatalities, especially if there is a preëxisting chronic ailment. Thrombophlebitis is the only complication of the severe cases.

A similar disease has also been reported in infants, children, and in adolescents. Adams¹ and his group have reported inclusion bodies in a "primary virus pneumonitis" seen in infants. Both the lungs obtained at postmortem and throat smears taken in life contained these inclusions in a high percentage of cases, whereas controls were usually negative. Using a wide variety of experimental animals, some not previously tried by other investigators, and including the technique of serial passages, they were unable to isolate a virus. Wall's excellent report⁶⁷ describes a similar pneumonia in children. In this group the mortality was high. The course was that of a typhoid-like illness in which roentgenograms showed a shifting bronchopneumonia with paradoxical physical findings, much as in ornithosis and adult human atypical pneumonia. Daniels¹³ also described a mild form of atypical pneumonia in young girls, his cases differing in that there were no prodromata before acute onset.

Bacteriology of Atypical Pneumonia. As we have seen, the virus of psittacosis was the first to be isolated.^{7a,b} In 1937 Burnet and Freeman¹¹ recovered a rickettsia from patients with Australian Q fever. Later Smith⁶⁰ showed that a potential Q fever reservoir existed in the ticks infesting the small animals of northern Australia. In 1940 Dyer, Topping, and Bengston¹³ recovered a rickettsia from the spleen of a fatal case of atypical pneumonia. Dyer's rickettsia gave cross immunity reactions with both Burnet's Q fever virus and that of American Q fever.¹⁴ There was no cross immunity, however,

with known strains of typhus of Rocky Mountain spotted fever virus. The same year Eaton, Beck, and Pearson¹⁹ recovered from the lungs of 2 fatal cases of atypical pneumonia a psittacosis-like virus which was highly mouse-virulent, but had a low virulence for the rice-bird and would not produce a carrier state in either host. This would indicate a relatively homogeneous infection chain not fully established in man. By complement fixation and mouse protection tests, Eaton's virus was found to be antigenically related to psittacosis as well as to another virus isolated in 1938 from the throat washings of a febrile catarrh patient by Francis and Magill.²³ Serologically it was distinct from influenza virus, from lymphocytic choriomeningitis virus, and from the virus of lymphogranuloma inguinale. In mice, ferrets, and monkeys, it produced an extensive pneumonitis on intranasal inoculation, and lymphocytic choriomeningitis on intracerebral inoculation. In 1941 Harrop, Rake and Shaffer²⁸ reported an atypical pneumonia occurring in laboratory personnel due to the lymphogranuloma virus with which they were working. Using the complement-fixation test they found cross reactions in their sera between the virus of lymphogranuloma inguinale, psittacosis virus, the Eaton virus, and Francis and Magill's meningo-pneumonitis virus. Five of 8 other cases of ordinary atypical pneumonia studied by Harrop's group had a positive Frei test. From the work of this group,⁵² it is now known that these viruses seem to have a similar type of developmental cycle, in some stages of which infectiousness is slight or absent, and in other stages of which the filter-passing power diminishes. All have multiple tropisms. In mice injected intracerebrally, they produce meningitis; intranasally, an identical pneumonia, and subcutaneously, similar granulomas. Most recently, Stickney and Heilman⁶² have recovered another ornithosis-like virus from a patient exposed to chickens and presenting the clinical picture of human atypical pneumonia.

Many other workers, however, have not had the success reported above. Weir and Horsfall⁷¹ exhausted a long list of animals before finding that the mongoose was apparently susceptible to human atypical pneumonia. Adams and his group¹ were without success, using an even greater variety of animals. Similarly, Enders²⁰ has inoculated the usual laboratory animals, including monkeys, by a variety of routes without success. Yet, despite these failures, the disease is readily transmitted from person to person.

These results lead to interesting speculations. If it is true that bacteria-free atypical pneumonia other than ornithosis was not known before 10 years ago, one of the ornithosis viruses might be offered as the progenitor of human atypical pneumonia, having become so established as a result of the 1929-30 psittacosis epidemic. This presumes a very rapid adaptation in man. It is more likely, however, that atypical (virus) pneumonia is an ancient disease.

As in endemic Australian ornithosis, perhaps some strains of the virus of human atypical pneumonia are well adapted to homogeneous human infection chains, while other strains, like the South American ornithosis virus, still require heterogeneous hosts to insure their perpetuation, and therefore may be passed to experimental animals.

Clinical Aspects of Ornithosis. Epidemiology. Normally the disease is contracted from sick or dying birds who show characteristic signs of the infection: cough, rhinitis, ruffled feathers, and sometimes diarrhea.³ Carriers are able to transmit the disease when their infected droppings dry and are blown about as dust, or if the birds are handled or allowed to feed from one's mouth. Occasional cases of human to human transmission are on record.^{29,30,43a} A second attack of psittacosis is also possible.^{43b,61}

Incubation Period. The usual interval between exposure and acute onset is 10 to 14 days, with a range of 8 days (as in the case Hoge²⁹ reports of a man bitten by a parrot) to 30 days.^{43a,61}

Prodromata. The onset is that of a rapidly developing, generalized infection with many findings characteristic of the typhoidal state. Within 1 to 3 days the temperature climbs rapidly to 104° F. or more. There is general malaise, a severe headache, often occipital at first and later frontal, great asthenia, and frequently the muscle aches of grippe. Nausea and vomiting occur, but diarrhea is rare. In the milder cases, epistaxis is present occasionally.

Signs. During the early stage of the illness, the striking findings are a relatively slow pulse of 80 to 100, a temperature of 102° to 105° F., mental torpor, a furred tongue, mild distention (in the more severe cases), and no localizing signs on examination.

Laboratory Data. The initial white blood count is normal or low, with 65 to 90% segmented neutrophils. There is often a mild proteinuria. A moderately elevated sedimentation rate which rises during the course and non-specific bacteriologic findings in the throat, blood, and stool are the rule. Secondary beta streptococcus sore throats or other infections may cause an elevated white count in their own right.

Clinical Course. Three types of the disease are encountered: (1) The very mild type of infection, lasting from a few days to 1 or 2 weeks, and occurring most often in adolescents and young adults. The prodromata and onset may be the same as in the severe cases. Headache, malaise, muscle aches, an unproductive cough, a negative physical examination, and minimal central pneumonia found by roentgenogram characterizes the illness. With daily roentgenograms Rivers⁵⁷ found that the hilar shadow appears with the acute symptoms but is represented by physical signs only after the 3d day.

(2) The typhoidal type, with variable pneumonic features, occurs most often in young adults and lasts 3 or 4 weeks. A dry cough and severe headache are the most prominent symptoms. Photo-

phobia or meningismus may be present. The temperature remains high with minor daily fluctuations. A relative bradycardia, distention, and constipation are common during the first week. The pneumonia is characteristically a patchy—at first usually central—migrating pneumonitis varying in density from the mottling of pulmonary congestion to the frank consolidation of lobar pneumonia. Atelectatic and asthmatic episodes, and paradoxical physical findings in the chest are common. Pleurisy or effusion are rare, although the signs may seem to indicate either. A secondary rise in temperature with further pneumonia may occur.

(3) The third type of the disease differs chiefly in its more widespread pneumonia, longer course, and more severe symptoms. In this group a mortality ranging up to 30% is present. Older age groups and those with underlying chronic disease are commonly attacked. Cyanosis appears early, even while respirations are slow and free. Delirium and terminal stupor are almost constant findings. Relapses are common, and thrombophlebitis and arteritis of the pulmonary vessels are complications. Occasional patients may show encephalitic symptoms with minor changes in the spinal fluid. When death does occur, it is from pulmonary insufficiency and generalized toxemia.

Pathologic Anatomy. Beyond an acute splenic tumor, pneumonia is the chief pathologic finding. Grossly the lungs show a diffuse confluent bronchopneumonia, usually beginning in the hilar regions and extending fanwise toward, but not often involving, the pleura. There may be a thick layer of crepitant lung over the dense areas, or an apparently consolidated lung may be air-bearing enough to float. This probably accounts for the paradoxical physical findings. In the early stages the pneumonic area is deep red. Later this changes to a greyish-red color. The bronchioles contain a tenacious exudate, and the alveoli a frothy hemorrhagic fluid suggestive of pulmonary edema.

Microscopically, there is a bronchiolitis with a neutrophilic and macrophagic exudate. The bronchial lining remains intact, and in places may be thrown into folds with a wild proliferation of cells resembling a carcinoma. During the acute stage, adjoining alveoli are engorged and contain various amounts of fibrin, red cells, and mononuclear cells. In the older lesions there is a thickening of the alveolar walls, due to widened lymphatics, engorged capillaries, and folding of the respiratory epithelium in which many mitotic figures are seen. An occasional vein shows thrombosis with a few neutrophils in its walls. With the proper stains it is possible to demonstrate the inclusion bodies of ornithosis containing the characteristic coecal *Microbacterium multifforme psittacosis* (M.M.P. bodies) in the epithelium.

The following cases are examples of the varying degrees of severity with which ornithosis may manifest itself.

Case Reports. CASE 1* (Fig. 1, Chart 1). L. J. (Med. 61028), a 41-year-old housewife, was admitted to the hospital December 16, 1941, with the complaints of malaise, headache and fever of 2 weeks' duration. She was known to have rheumatic heart disease. Two weeks before coming to the hospital she noticed general muscle aches, malaise, sore eyeballs and occipital headache. After 4 days the headache became postorbital, there was photophobia, and she developed a dry, hacking cough. On the 7th day the family physician found her temperature to be 101° to 103° F. Progressive asthenia, shortness of breath and orthopnea developed, and on the 14th day auscultatory signs of pneumonia appeared in the chest. Because of this she was sent to the hospital.



FIG. 1.—Mild case of ornithosis; 14th day of disease. Roentgen film of chest.

Physical Examination. The temperature was 103° F., pulse 96 per minute, respirations 25, and the blood pressure 112/74. The patient was flushed, perspiring freely and apparently acutely ill. Despite moderate orthopnea, respirations were quiet and free. The tongue was coated and the pharynx slightly injected. The percussion note of the chest was not altered; however, over the right upper lobe posteriorly there were increased pectoriloquy, increased breath sounds, and many fine crepitant râles. The heart was enlarged to the left, and at the apex there was a Grade III systolic murmur.

* Patient under the care of Dr. Harry Blotner; seen in consultation by author.

Laboratory Data. Urinalysis and stool examination were negative. The initial white count was 4700 (64% neutrophils). Four subsequent counts were below 5200 with a normal differential. The hematocrit reading was 21, hemoglobin 66% (Sahli), and the sedimentation rate 65 (Wintrobe uncorrected). The red cells showed a hypochromic microcytic anemia. Blood cultures were negative. Sputum showed no acid-fast organisms on smear or *pneumococci* on culture. A Frei test the third week of the illness was negative.

Course. On entry, the patient was started on sulfadiazine. Gradually the temperature returned to normal, but not as promptly as is expected with chemotherapy. The chest cleared correspondingly. On the 8th hospital day the blood sulfadiazine level was 24 mg. per 100 cc. The dose was cut, but by the next day the urine output fell to 550 cc., the temperature

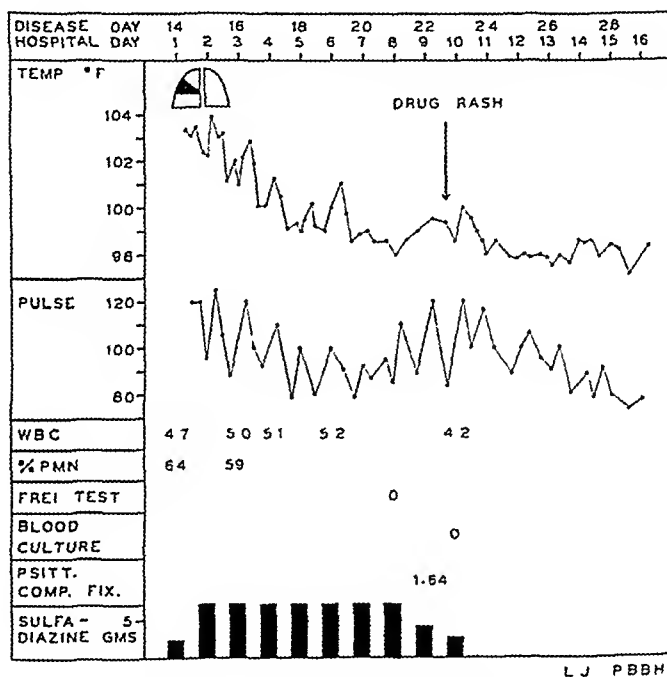


CHART 1 —Clinical chart. Case 1.

rose slightly, a large number of crystals were seen in the urine, and an erythematous, maculopapular, puritic eruption appeared on the arms and trunk. A repeat blood level at this time was 4 mg. per 100 cc. Within 2 days the rash was gone. Convalescence was uneventful.

Epidemiology of Case. In the early part of October, 1941, about 2 months before the patient's illness, her husband started a pigeon loft. Shortly after acquiring the second pair of birds, one became ill with diarrhea. This bird was exchanged for a healthy king bird (pigeon). A week and a half later the family Pomerian developed anorexia, fever, the shakes, and a paroxysmal cough which often promoted vomiting. This illness lasted 2 weeks. Two weeks later another pigeon was added to the flock, and although purchased from a different dealer it developed ruffled feathers, diarrhea, and what the patient thought was "whooping cough." Every day she went into the bird house to water the pigeons. The only contacts with the birds were the

clouds of dust they raised, which were often enough to drive her out in the open. Two weeks after the second sick bird showed symptoms, and when the bird itself had almost recovered, the patient noticed general muscle aches, malaise, sore eyeballs, and occipital headache.

The establishment from which the second sick bird was purchased was visited by the author, but found to have gone out of business. The patient's birds were set free on Christmas day by the husband in a fit of gloom over his wife's long illness. The dealer who supplied the first sick bird was also visited and found to have a large outdoor aviary. He explained that his birds were quite healthy, but that occasionally one would develop diarrhea, look seedy, and die. This usually took place in the fall and early winter. At the time of the visit, the early spring, all the birds were sleek. Nevertheless, 6 pigeons, including 2 young ones and the thinnest birds to be found, were selected and their spleens removed. One adult spleen appeared to be about twice the normal size. Impression smears stained by Castaneda's technique did not show inclusion bodies. The spleens were ground together and inoculated intraperitoneally in mice. So far, splenomegaly in an occasional mouse is all that passage seems to produce.

On the 4th week of the illness, and again 2 months after recovery, serum was taken from the patient. The family dog and the husband were also bled. Dr. K. F. Meyer was kind enough to do complement-fixation tests for psittacosis on these samples. There was 4+ complement fixation to a dilution of 1:64 on both of the patient's specimens. The dog and husband were negative. This is consistent with a diagnosis of psittacosis in the patient.

Summary of Case. The patient, a 41-year-old housewife with rheumatic heart disease, came to the hospital 2 weeks after the onset of an illness characterized by headache, fever, malaise, weakness, and a dry cough. The temperature was 103° F., pulse 96 per minute, and there were minimal signs of pneumonia in the right upper lobe. Roentgen ray confirmed the physical findings. The white count was always below 5200. There was a moderately severe hypochromic microcytic anemia. Routine bacteriology was negative. Sulfadiazine had little, if any, effect on the course, other than to produce a temporary oliguria, rash and fever. Recovery was prompt without complications other than the concurrent cardiac disability. Serum sent to Dr. K. F. Meyer gave a diagnostic elevation of complement fixing antibodies for psittacosis.

CASE 2 (Figs. 2, 3, 4; Chart 2). H. R. B. (Med. 61013), a 44-year-old unmarried clerk, was referred to the hospital December 12, 1941, by his family physician because of a pneumonia which did not yield to sulfonamide medication. For an indefinite time the patient had been overworked and run down. Thirteen days before entry there was nausea, vomiting, and a shaking chill lasting 10 to 15 minutes, followed by alternating chilliness and feverishness. The next day a hacking, non-productive cough set in, and on the 3rd day the patient's doctor found auscultatory signs of pneumonia, for which he prescribed prontosil 3 to 4 gm. a day. On the 7th day the temperature was 103° F., the pneumonia unchanged, and for this reason sulfathiazole was tried. It too had no effect, and on the 13th day the patient was sent to the hospital. Throughout, a severe frontal headache had been one of his most troublesome symptoms.

Examination. The temperature was 104° F., pulse 100 per minute, respirations 24, and the blood pressure 135/70. The patient was mentally

confused, perspiring freely, breathing easily, and acutely ill. The slight exertion of moving or talking precipitated unproductive paroxysmal coughing. A few pea-sized cervical lymph nodes were palpable. There was suffusion of the conjunctivæ, a furred tongue, and moderate inflammation of the pharynx. At the right base there was dullness to percussion, increase in tactile fremitus, bronchial breathing, and suppression of breath sounds. At both bases there were moist inspiratory and expiratory râles. The abdomen was distended. The liver and spleen could not be felt. Reflexes were physiological.

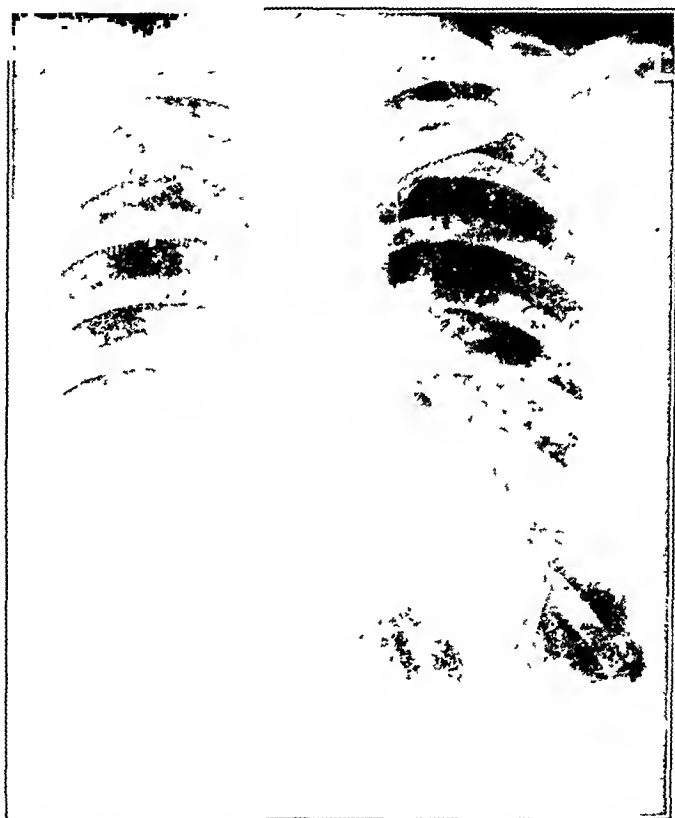


FIG. 2.—Severe ornithosis (Case 2); 13th day of disease. Roentgen film of chest

Laboratory Data. Except for occasional microscopic hematuria, the urine remained clear. With a hematocrit of 44, the sedimentation rate was 48 mm. per hour (Wintrobe uncorrected). It remained in the 50's during the first hospital week and was 30 in convalescence. The initial white count was 15,000 with 79% polymorphonuclears. Subsequent counts fluctuated between 7300 and 12,000, with much the same proportion of polymorphonuclears. The initial stool, which was liquid, gave a 1+ guaiac test. Later specimens were normal. Blood, stool and throat cultures were non-contributory. A Frei test (Lygranum) on the 25th and 40th days was negative. The chest Roentgen ray showed a soft hilar shadow extending into the base and a partial consolidation of the right middle and lower lobes. A week later the right base was clearing, and a fine granular mottling

suggesting edema was present in all but the left upper lobe. As this cleared, the left upper was involved.

Course. The course was long and stormy. The high fever, relative bradycardia, characteristic cough, slight cyanosis, headache, and abdominal distention could only be treated symptomatically. Sulfadiazine was given without effect. The physical signs were always less than indicated by Roentgen ray. Râles did not disappear until the patient was afebrile. At the end of the 2d hospital week a basilar friction rub was heard bilaterally for a short while. Convalescence was complicated by a thrombophlebitis with persistent varicose veins requiring an Ace bandage.

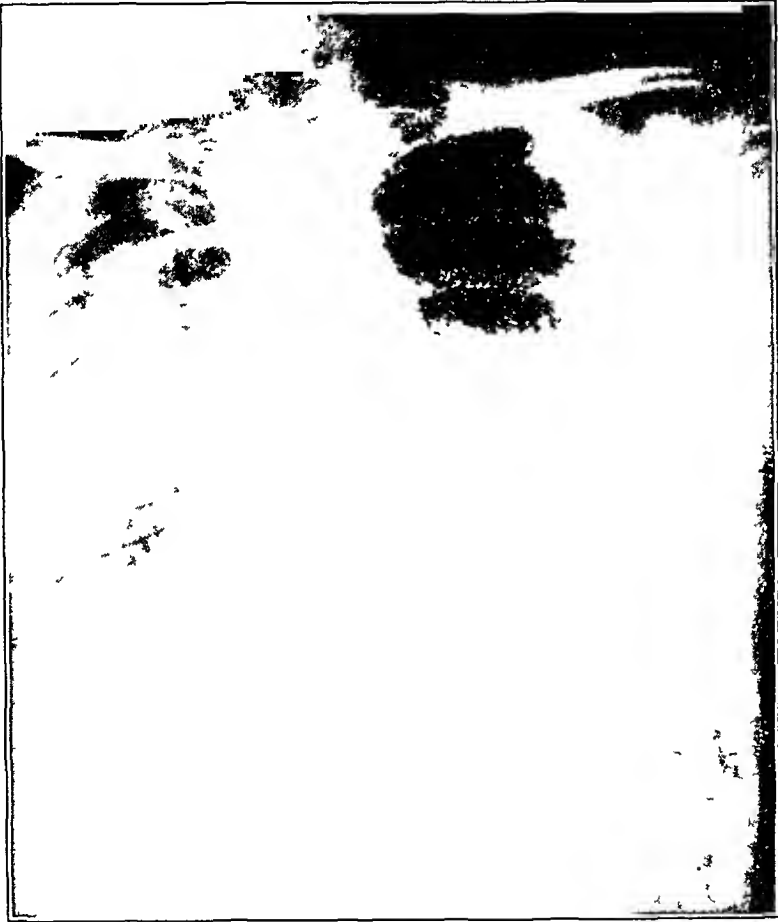


FIG. 3.—Case 2; 16th day of disease. Roentgen film of chest.

Epidemiology of Case. For years the patient had kept bachelor quarters on Beacon Street with a friend who had bronchial asthma. Within the last year the roommate had not had any acute illnesses. During the past 5 years the two bachelors had had a trained canary in the house, who at times was allowed to fly about the room, to walk up their arms, and to take food from their mouths. About a year ago the bird also developed asthma, and soon after a cyst appeared over one eye. The tumor enlarged gradually, and in the first week of November, 1941, the bird developed greater wheezing, a cough, diarrhea, ruffled feathers, and died. The patient cremated the canary and cleaned the cage approximately 3 weeks before the onset of his illness. A week after the canary died the patient purchased 2 new

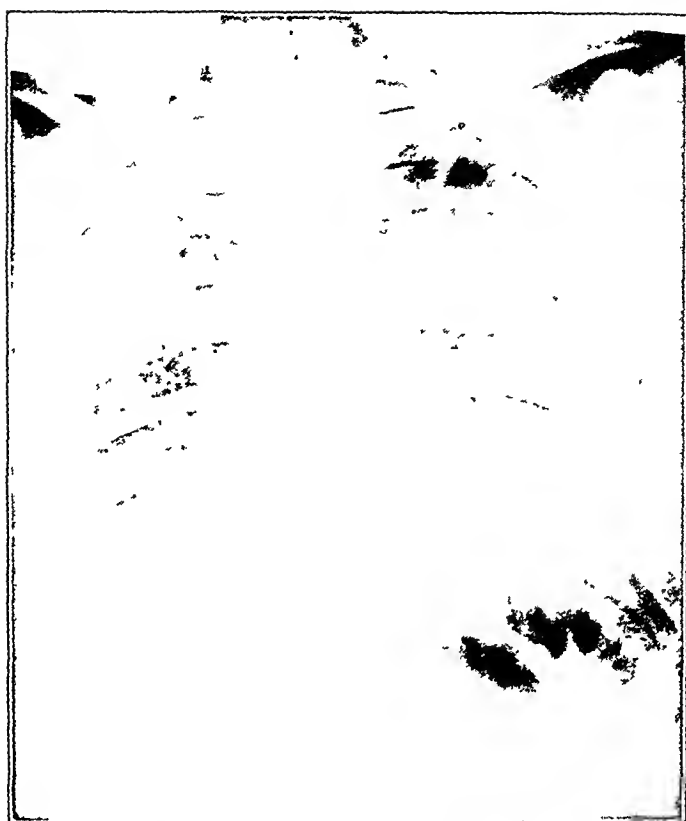


FIG. 4 —Case 2; 19th day of disease Roentgen film of chest

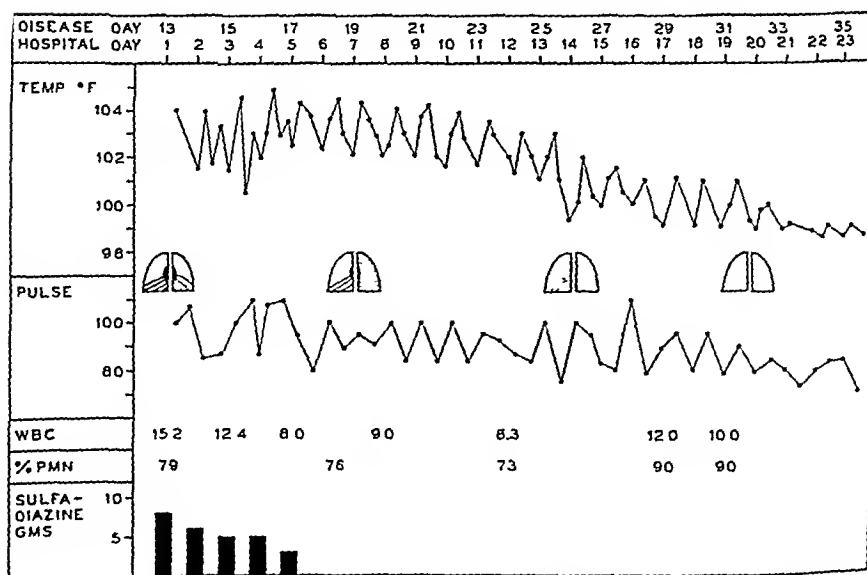


CHART 2.—Clinical chart, Case 2.

canaries. These were always healthy, and the pet shop from which they came gave no history of sick birds. Subsequently the birds were sent to the National Institute of Health in Washington, where no evidence of infection was found.

Serum was collected from the patient and from the roommate on the 14th and 43d days of his illness. These samples were sent to Dr. K. F. Meyer in California, who reported 4+ psittacosis complement fixation to a dilution of 1:128 and 1:256 on the patient's sera respectively, and 1:8 on that from the roommate. The patient's high titer is good evidence that his illness was psittacosis. The low titer in the roommate indicates a latent infection.

Summary of Case. This 44-year-old clerk came to the hospital after 13 days of an acute illness beginning with severe headache, shaking chills, a hacking non-productive cough, nausea, vomiting, and developing into a pneumonia which would not respond to sulfonamides. He had disposed of a dead canary 3 weeks before symptoms. There was a stormy course lasting a month, during which time a migrating pneumonia was the most important finding. The white count was moderately elevated and the bacteriology negative. Abdominal distention, mild delirium, cyanosis, persistent high fever, with at first a relative bradycardia and later a tachycardia, and a non-productive cough characterized the course. Convalescence was complicated by thrombophlebitis and persistent varicose veins. A high and rising titer in his serum and a low titer in his roommate's serum of psittacosis complement-fixing antibodies confirms the diagnosis of active psittacosis in the patient and a latent infection in his friend.

CASE 3 (Figs. 5, 6, 7; Chart 3). M. C. B. (Med. 59613), a 41-year-old married, colored postal clerk, was admitted to the hospital May 2, 1941, with the complaints of headache and fever of 5 days' duration. During the evenings the patient worked as a postal clerk and during the days attended law school, studied, and slept. For the 2 weeks before coming to the hospital he had assumed the additional burden of preparing for a civil service examination. Six days before entry the patient went to the beach without warm enough clothing. That evening he developed a severe headache, and by the next day complained of general malaise and a shaking chill. From the 2d to the 4th days before coming in there was progressive weakness, malaise, and finally chills and fever. Despite these symptoms the patient remained ambulatory, and on the night before hospitalization took the examination for which he had been preparing. During this time cough was negligible and sputum scanty. However, headache and burning behind the eyes were severe.

Examination. The temperature was 104.6° F., pulse 92 per minute, respirations 24, and blood pressure 130/85. The patient appeared only moderately ill. Respirations were free and painless. Several small shotty lymph nodes were palpable in the anterior cervical triangles. The nose was clear, the tongue furred, the pharynx negative, and the neck supple. Over the upper right lung posteriorly there were diminished breath sounds and a few fine râles. The heart was normal. The spleen could not be felt, but the liver was palpable 2 fingers below the costal margin. The abdomen was mildly distended. Neurologic examination was normal.

Laboratory Data. The urine showed 1+ acetone in the first specimen and from 0 to 2+ albumin in many subsequent specimens. One to two

white cells were seen in the sediment on several occasions. The hematocrit reading was 48, later falling to 43, hemoglobin 16.3 gm., and the sedimentation rate 13 mm. per hour (Wintrobe uncorrected). On admission the white count was 10,000 with 85% polymorphonuclears. At the height of the illness it rose to 16,000 with 95% polymorphoneuclears, and in convalescence was 9000 with 85% polymorphonuclears. Stool, urine, and blood cultures were non-specific. Agglutinations with *B. tularensis*, *suipestifer* H, typhoid (H and O), paratyphoid B, *proteus* X19 and OXK, and *brucella* antigens were negative both at 1 and 4 weeks. Lung puncture material and spinal fluid were sterile aerobically and anaerobically. Intraperitoneal



FIG. 5.—Probable ornithosis (Case 3); 7th day of disease. Roentgen film of chest.

inoculations of sputum into mice and guinea pigs produced no disease in these animals. The total proteins during the acute phase of the illness were 7.5 gms. per 100 cc. A Frei test early and late in the disease was negative.

Course. During the first week the temperature persisted at 105° F.; there was a relative bradycardia, severe headache, and a progressive torpor with accompanying stiff neck. Several lumbar punctures at this time revealed The diagnosis of pneumonia was confirmed by Roentgen ray, which showed a broad zone of consolidation involving the lower portion of the right upper lobe. Abdominal distention was combated with difficulty. Sulfathiazole had no effect. At the height of the illness a thoracentesis yielded 10 cc. of clear sterile fluid,

and 3 days later a lung puncture was equally negative, both by culture and inoculation into mice. Sulfapyridine was then tried, but was also without effect. The pulse rose, and tachycardia persisted throughout convalescence. With the onset of a fast pulse recovery began, and by the 19th hospital day the temperature was normal.

From the beginning, the physical chest signs were always less than the Roentgen ray findings. At no time was there absolute flatness nor was there frank tubular breathing, although the paradoxical signs of fluid led to a relatively dry chest tap. Clearing was a gradual process with râles persisting until the temperature was normal. The spleen was never felt



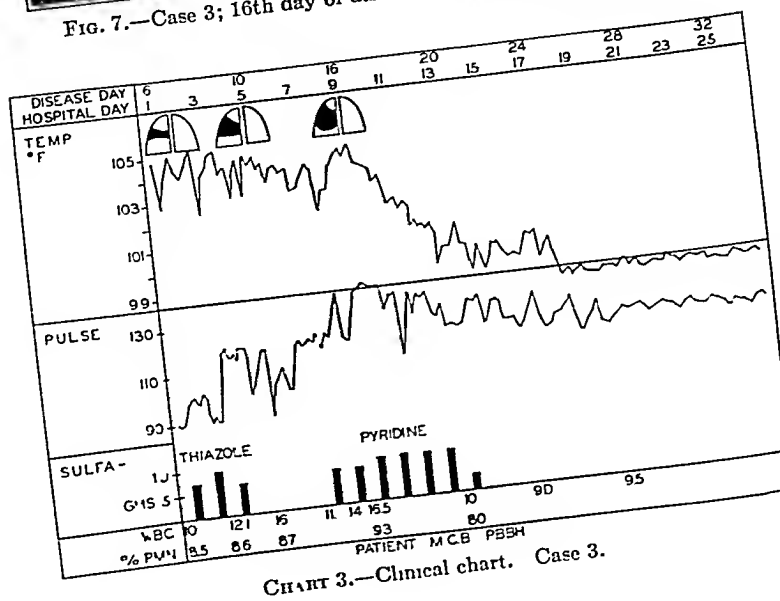
FIG. 6.—Case 3; 10th day of disease. Roentgen film of chest.

and the liver receded with recovery. Repeated Roentgen rays revealed a spreading pneumonia confined chiefly to the right lung field. Recovery was uncomplicated, and now, a year later, the patient is quite well.

Epidemiology of Case. No history of pets, birds, or animals as contacts could be found, nor was a person-to-person infection chain evident. Serum taken 2 weeks after defervescence was found to have a positive complement fixation for psittacosis $4+ 1:8$ and $3+ 1:16$. Serum taken 11 months after infection at which time the patient was in excellent health had a psittacosis complement-fixation $4+ 1:64$. This is suggestive of psittacosis.



FIG. 7.—Case 3; 16th day of disease. Roentgen film of chest.



Summary of Case. This 41-year-old postal clerk came to the hospital on the 6th day of an acute febrile illness characterized by persistent sulfonamide-resistant temperatures of 105° F., a relative bradycardia, a large area of consolidation in the right lung, a white count of 10,000 with 85% polymorphonuclears, and no cough or sputum. Extensive laboratory work did not implicate any of the usual causes of acute pneumonia. The course was stormy with a high white count and tachycardia during convalescence. Serum taken after recovery contained a significant titer of complement fixing antibodies for psittacosis.

Discussion. During the 1½ years in which the above cases of ornithosis were observed, we have had more than 12 cases of human atypical pneumonia, representing all the clinical types of the group from the rapidly fatal fulminating infection to the mild case with an unsuspected patch of consolidation found only on Roentgen ray examination of the lungs. In every case it has been possible to match the clinical picture and course of these human atypical pneumonias with that which has been outlined for psittacosis. The same parallel is evident in the larger series reported by Murray,⁴⁷ Longcope,³⁷ Reiman,^{53,54} and others.

Except in localized outbreaks where contacts are known, atypical (virus) pneumonia seems to be a sporadic infection arising unheralded, as though either the patient himself had a latent infection which was activated by unfavorable physical or environmental conditions, or the disease was transmitted by carriers who themselves had only a mild headache or a simple afebrile tracheobronchitis. Again and again we have been impressed by the history of another member of the family having an episode of headache and dry cough 2 to 3 weeks before the patient became acutely ill with atypical (virus) pneumonia. It is also of interest that the fall and early winter are the most common seasons of attack of both pneumonia and the non-bacterial tracheobronchitis. This is entirely analogous to the frequency of ornithosis infection in birds with the onset of the cold weather, when the disease is activated in carriers and new and more fulminating infections begin to appear in other birds.

Where the incubation period of "atypical pneumonia" is known,^{33,37,47} the range is 7 to 21 days, with a usual time of 11 to 14 days. This is identical with the incubation period for ornithosis. We know also that infectiousness in virus pneumonia may be as great as in ornithosis. Nurses have been known to come down with atypical pneumonia 2 weeks after working one day on an isolation ward with atypical pneumonia patients, where masks, gowns, and goggles were routinely worn for protection.²¹ Similarly, ward patients in the next bed, doctors, and Roentgen ray technicians have been infected after brief contact with a case of atypical pneumonia.^{21,37}

The prodromata of "atypical pneumonia"^{33,37,47,59} are the same as those for ornithosis. In atypical pneumonia there is usually a 1- to 3-day onset with malaise, chilly sensations, or occasionally a frank shaking chill. Cough may initiate the illness and often there is minimal coryza with occasional epistaxis. Nausea, vomiting, and diarrhea are uncommon. Acute symptoms are preceded by a rapid rise in temperature to 104° F. with a relative bradycardia. A hacking cough and severe headache are almost constant symptoms.

The signs of "atypical pneumonia" are the same as those of ornithosis. A typhoidal languor, photophobia, conjunctival suffusion, and mild coryza are usually present. The tongue is furred, and unless there is a superimposed streptococcal pharyngitis, the throat is benign. Occasionally glandular enlargement, rashes or a meningitis are seen. Much the same early signs are characteristic of ornithosis.

The comparison is equally good between the laboratory data in the two conditions. In "atypical pneumonia" the white count is low or normal, with 70 to 90% segmented neutrophils. Initially there may be a mild albuminuria and a low sedimentation rate. During the course the sedimentation rate rises to 30 or 40 mm. per hour. Routine cultures of the blood, throat, stools, sputum, and throat washings usually do not yield any pathogenic organisms in abundance. If the course is rapidly fatal in either ornithosis or atypical pneumonia, the white count may be 20,000 or more, as we observed in one of our atypical pneumonia patients who died on the 11th day.

The cases of either disease may be classified into 3 general clinical types of severity. There are the very mild infections⁴⁷ lasting 1 to 7 days, occurring in young adults and characterized by malaise, muscle aches, headache, and a variable amount of non-productive cough. Physical examination is negative the first 3 days, although a Roentgen ray of the chest will show a central pneumonia. A few chest findings may appear on the 4th day, or the patient may recover without developing the signs of pneumonia. Sometimes the atypical pneumonia patients show an elevation in the white count to 17,000 or more during recovery. In ornithosis it does not often rise to as high a level.

The more severe type of infection, common in the older age groups, with both "atypical pneumonia" and ornithosis the course may run for one or more months. In each disease there is a typhoid-like state and a migrating pneumonia, a high temperature with minor fluctuations, and a tendency to relapse. Usually children under 10 do not contract ornithosis on exposure; however, atypical pneumonia has been described as a severe childhood infection and is especially fatal in infants. In both diseases relative bradycardia for the first week or more, later giving way to a normal or fast pulse, constipation, and distention, are consistent findings. Languor.

severe headache, and a paroxysmal dry cough persist throughout. The pneumonia in both diseases is alike. It is a central, patchy, migrating pneumonitis, usually giving fewer physical than Roentgen ray signs. The density is either a fine mottling, an atelectasis, or frank consolidation. Cyanosis out of proportion to the area involved, and asthmatic episodes, often complicate the picture.

The third type of "atypical pneumonia," characterized by either a rapidly fatal spreading pneumonia with dense consolidation or a long course with a predilection for the age extremes or those with underlying chronic disease, and characterized by a migrating pneumonia and high fever, is similar to the very severe form of ornithosis. A variety of bizarre manifestations may also be present in atypical pneumonia. Migrating polyarthritis, erythematous skin eruptions, jaundice, hematuria, fibrinous pericarditis, general glandular enlargement, encephalitis, and thrombophlebitis occur. In all types of both ornithosis and atypical pneumonia it is interesting that the Roentgen ray changes may persist from a few days to weeks after the patient becomes afebrile.

Pathologically the findings in "atypical pneumonia" are very similar to those of ornithosis and other known virus pneumonias. It is as if the body tended to respond in a similar manner to a variety of closely related but distinct pathogenic agents. Grossly the lungs in atypical pneumonia may show loose adhesions connecting the lobes and a fibrinous exudate over the visceral pleura. A patchy consolidation resembling confluent lobular pneumonia, areas of atelectasis, or what appears to be pulmonary edema, may be present. The small bronchi contain a thick mucopurulent exudate consisting chiefly of polymorphonuclear leukocytes, and show congestion of their mucosa. The early lesions are a hemorrhagic alveolitis and an interstitial bronchitis and tracheitis, with squamous metaplasia and segmented neutrophilic infiltration in the bronchi, and a mononuclear response in the alveoli. These are almost identical with the findings in ornithosis. In the later stage of atypical pneumonia, the septa become thickened by rows of mononuclear cells about the alveolar periphery, which infiltrate the septal walls, as well as by a tendency to organization with fibroblastic and endothelial cell proliferation. The most interesting findings of atypical pneumonia are vascular and perivascular lesions in the lung capillaries and in the medium-sized branches of the pulmonary arteries, showing a neutrophilic, mononuclear, and eosinophilic infiltration, reminiscent of periarteritis nodosa.

Two of the patients presented in this report had a high titer of psittacosis antibody in their immediate convalescent serum. The third had a convalescent titer which was moderate, and well may represent a cross-reaction so common in this general group of infections. The same complement-fixation test for psittacosis has been done on most of our other "atypical pneumonia" cases, and in all cases there has

either been a negative reaction, or at most positive fixation in dilutions of 1:2 during the late acute phase of the illness. None have shown a rise in titer nor positive fixation during convalescence. Other serologic procedures are needed in studying this type of infection to detect the presence of latent infections as well as outspoken cases of human "atypical pneumonia." Only then will it be possible to show how endemic in man is "atypical pneumonia" and what can be done to control it.

In the absence of such tests we must continue to classify bronchopneumonias as primary bacterial, mixed bacterial and interstitial, and interstitial (or "atypical pneumonia"). Before the clinical differentiation of a group of pneumonias similar to psittacosis, most bronchopneumonias were lumped together as the same disease process. Now there is considerable doubt whether some of those cases, from which the high numbered types of *pneumococci* are recovered and in which there is only a moderately elevated white count, are simple bacterial bronchopneumonias, especially when chemotherapy has little effect. What they probably represent are various combinations of bacterial and virus invasion, much as is the case with influenza. In any one patient there may be a predominance of the bacteria or of the virus. It is not unusual for mixed as well as pure interstitial bronchopneumonias to be incited by conditions which lower the state of physical fitness, such as operations, chronic diseases, great fatigue, or other acute illnesses, much as the change of seasons brings out ornithosis in birds or atypical pneumonia in man. The practical point is to limit sulfonamide therapy to cases where there is significant secondary bacterial invasion, since it is not effective in either ornithotic or human atypical pneumonia.

Within the group of atypical pneumonias themselves great confusion has arisen from the failure of simple or extensive laboratory techniques to reveal a single etiologic agent. Recently, however, serologic work had tended to relate the several different viruses which have been isolated from human cases. Our new knowledge of the ecology of ornithosis has suggested an ecology of atypical pneumonia in man. Except for a demonstration of latent atypical pneumonia infections, the two diseases are similar. Some strains are high in infectivity, mortality, and ability to take on a heterogeneous host, while others may infect only the age extremes or the chronically ill and will not take on any other known host. It is just as significant that good workers are unable to isolate a virus pathogenic for laboratory animals in many human patients as it is that in other patients they have found 4 or 5 related viruses, all capable of producing the same disease picture.

The cases presented in this report are also of interest because a variety of animal inoculations did not differentiate ornithotic pneumonia from the human type of virus pneumonia. If we had

not had the assistance of Dr. K. F. Meyer's laboratory, where the psittacosis complement fixations were done, all cases might have been regarded as human virus pneumonia. Furthermore, we would have missed the fact that ornithosis is probably much more common than is suspected. It is significant that the history of bird contact, where found, was always obtained several days *after* the patient had been in the hospital, and was sought chiefly because the hospital staff had been awakened to the ornithosis problem by a visit from Dr. Meyer.

Summary. 1. "Acute atypical pneumonia" is defined as a form of interstitial bronchopneumonia, not usually accompanied by secondary bacterial invasion, and characterized by bradycardia, headache, dry cough, low or normal white count, and failure to respond to the sulfonamides. While the term may well be used where no etiologic agents have been identified, when they can be isolated from cases of this type, they are found to belong to a related group of viruses.

2. The first isolated example of this type of pneumonia is psittacosis or ornithosis. Its history is traced from its initial description in 1879, through the discovery of its virus etiology in 1930 during the international epidemic, to the ecologic investigations of the last few years.

3. Interstitial pneumonia has been described in cases of influenza, measles, pertussis, and varicella, and in these instances may be due entirely to the action of either a virus or a bacterium, or frequently to a combination of the two. It has also been observed in the course of acute rheumatic fever (rheumatic pneumonia) and after irradiation of the thorax, and for that reason probably represents a pathologic response to a number of types of pulmonary irritants.

4. Comparison of the incubation period, symptoms, clinical course, pathologic and laboratory findings in ornithosis (psittacosis) with those in the human atypical pneumonia group reveals very striking similarities. The results of virus studies and serologic tests in these diseases also indicate this close relationship.

5. One probable and 2 definite cases of ornithosis observed in the course of 18 months in Boston are presented.

6. The frequency with which ornithosis virus may cause atypical pneumonia in man is emphasized. Careful questioning about contact with varieties of birds known to harbor the virus, and complement-fixation tests on acute and convalescent sera should be performed in order to make the diagnosis.

7. It is suggested that cases of human atypical pneumonia from which no etiologic agents have been isolated may be due to a virus of the psittacosis group which has become fixed in man and is usually incapable of heterogeneous parasitism.

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THE ABSORPTION RATE FROM THE BONE MARROW

BY LEO M. MEYER, M.D.

AND

MARTIN PERLMUTTER, M.D.

BROOKLYN, N. Y.

(From the Department of Medicine, Long Island College of Medicine and the Kings County Hospital)

SINCE 1940 the introduction of blood, plasma and other fluids into the medullary cavities of the sternum and long bones has been used for the parenteral injection of such solutions. The value of this procedure in cases of extensive burns of extremities, extreme shock with peripheral vascular collapse, and in small infants has been reported by Tocantins and O'Neill^{7,8} and Tocantins, O'Neill and Jones.⁹ That the fluids injected are rapidly absorbed was shown by the clinical improvement of the patients and also by experimental procedures, both in man and small animals.

In 1934, Josefson⁴ injected 4 to 5 cc. of Campolan intrasternally in cases of pernicious anemia and noted the reticulocytosis and

improvement in the condition of his patients. In 1940, Tocantins⁶ bled rabbits of 20% of their blood. One day later he injected an equal amount of blood into the marrow of the upper end of the tibia and found that the hemoglobin and red cells became normal in 24 hours. In a second experiment he rendered rabbits convulsive by the intravenous injection of insulin. The injection of 20% to 30% glucose into the tibial marrow produced a cessation of symptoms in 2 minutes. In a third experiment the author put one needle into a rabbit's heart and a second one into the tibia. Congo red solution was injected into the tibia and within 10 seconds the dye was found in the plasma from the heart's blood. Macht,⁵ using dogs, cats, rabbits, guinea pigs, rats and mice, showed that the effect of intramedullary injection of a large group of drugs was rapid, as indicated by their characteristic systemic effects. Tocantins, O'Neill and Jones⁹ also proved the rapid absorption of chemicals and drugs from the marrow by injecting Diodrast and obtaining Roentgen ray evidence of this dye in the renal pelvis of children 5 minutes later.

The pathway for the exit of solutions injected has also been investigated in man and animals. Benda, Debray and Bournee¹ in 1937 injected the femurs of guinea pigs with a radiopaque solution and demonstrated its generalized dissemination in all major blood-vessels. In 1940, Tocantins⁶ injected mercury into the tibial marrow of the rabbit and noted its appearance in the deep femoral vein. He also injected the same metal into the sternal marrow of a cadaver and at subsequent autopsy found the material in the internal mammary veins. Benda, Orinstein and Depitre² performed a similar experiment using thorium in the cadaver and lipiodol in the live patient, and on Roentgen ray both solutions were seen in the internal mammary veins. Henwig³ obtained the same result using an opaque dye. Tocantins, O'Neill and Price¹⁰ injected a rapidly hardening green solution into the sternal marrow of the cadaver, and at autopsy found the material extending from the marrow into the internal mammary veins and the right auricle.

In the present experiment an effort was made to determine in actual time the absorption rate from the marrow as compared with the injection of the same substance into the vein. Circulation times were done by injecting 3 cc. of a saturated solution of saccharin into the median basilic veins of 24 subjects. The length of time required for the injection, the time elapsing from the beginning of injection to the onset of tasting as noted by the patient are recorded in Table 1. The next step was the injection of an equal amount of the same solution into the sternal marrow of these same patients soon after the intravenous test. The site of injection was in the midline of the body of the sternum at the level of the third interspace. The marrow was first aspirated in order to insure the presence of the needle at the proper site. As indicated in Table 1, the length of time re-

quired for the injection and the time elapsing from the beginning of the injection to the onset of sensation of taste were noted. The resistance to injection varied in different subjects. The complaint of pain did not vary with the resistance encountered in introducing the solution, and was worse in the more sensitive patients. In some instances the pain was apparently very severe, radiating from the sternum around to the back. No subsequent ill-effects were observed.

TABLE 1.—LENGTH OF TIME FROM INJECTION TO TASTE

Name	Age	Arm to tongue		Sternum to tongue		Clinical diagnosis	Resistance	Pain
		Time to inject (sec.)	After injection (sec.)	Time to inject (sec.)	After injection (sec.)			
O. C.	56	3	13	6	12	Cirrhosis of liver	Sl.	Sl.
S. D.	52	6	28	7	22	Carcinoma of stomach	Sl.	Sl.
J. D.	76	5	20	5	18	Gout	None	None
S. F.	59	4	15	5	18	Pulmonary tbc.	Sl.	Mod.
L. N.	55	3	13	5	13	Obstructive jaundice	Mod.	Mod.
L. G.	41	4	15	8	15	Bronchiectasis	Mod.	Mod.
M. W.	45	3	15	4	15	Pulmonary tbc.	None	Sl.
A. W.	42	4	15	7	15	Bronchiectasis	None	Mod.
H. W.	52	3	13	7	15	Chronic alcoholism	Sl.	Mod.
E. L.	62	3	14	9	17	Osteoporosis of bone	Mod.	Mod.
J. Y.	48	3	20	7	22	Peptic ulcer	None	Mod.
M. W.	61	3	35	5	20	Pyelitis	None	None
R. S.	49	4	14	10	15	Gastric neurosis	Sl.	Sl.
J. D.	38	3	23	8	22	Pulmonary tbc.	Sl.	Mod.
M. P.	31	5	28	13	28	Rheumatic heart disease (compensated)	Mod.	Mod.
M. R.	35	3	10	10	18	Chronic osteomyelitis	Mod.	Mod.
L. B.	33	3	28	10	23	Cardiac decompensation	Sl.	Sl.
S. B.	58	3	12	6	11	Pulmonary tbc.	Sl.	Sl.
R. H.	24	2	13	10	14	Acute tonsillitis	Mod.	Mod.
T. C.	53	2	13	6	8	Pulmonary tbc.	Sl.	Mod.
A. N.	61	3	24	7	24	Cardiac decompensation	Mod.	Mod.
H. J.	16	3	13	13	13	Rheumatic heart disease (compensated)	Mod.	Sl.
J. B.	23	2	13	11	11	Acute nephritis	Marked	Mod.
G. D.	57	2	23	9	12	Cardiac decompensation	Mod.	Mod.
Average . . .		3.3	17.9	7.9	17			

A survey of the results obtained indicates a distinct consistency in the circulation time for the individual subject. In 2 of the 3 cases of cardiac decompensation which were selected, the circulation time from the marrow was less than by the intravenous route. Apparently the shorter distance the solution had to traverse when associated with a slowing of the circulation was a factor in obtaining these results. The authors feel that these experiments are a further proof of the intimate relationship between the bone marrow and the venous circulation, and that this immediate absorption justifies the intramedullary route wherever the rapid administration of fluids is required and the solution cannot be conveniently given intravenously.

Conclusions. 1. A comparison was made of circulation times using the intravenous and intramedullary routes and was found to be essentially the same in 21 subjects.

2. In 2 cases of cardiac decompensation the circulation time from

marrow to tongue was less than by the venous route. In a third case the results were identical.

3. These results are further proof of the intimate relationship between the medullary cavities and the general circulation, and warrant the use of intramedullary injection of fluids when venous channels are not readily accessible.

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THE USE OF OUABAIN IN RAPID CARDIAC ARRHYTHMIAS

By WILLIAM I. GEFTER, M.D.

RESIDENT IN MEDICINE, PHILADELPHIA GENERAL HOSPITAL

AND

WILLIAM G. LEAMAN, JR., M.D.

PROFESSOR OF MEDICINE, WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA, VISITING
PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL,
PHILADELPHIA, PA.

(From the Medical Division, Philadelphia General Hospital)

OUABAIN, first isolated by Arnaud in 1888, is approximately twice as potent as strophanthin.⁶

As the use of strophanthin as a method of rapid digitalization in congestive failure and in rapid cardiac arrhythmias is well established, and as Batterman, Rose and De Graff¹ have reported on the use of ouabain in congestive heart failure, we have endeavored to evaluate the use of ouabain in rapid cardiac arrhythmias. Thirty-three patients from the wards of the Philadelphia General Hospital* were studied. All had rapid cardiac arrhythmias, the ventricular rates ranging from 140 to 210 per minute. There were 2 cases of paroxysmal auricular tachycardia, 4 of auricular flutter, 24 of auricular fibrillation, 2 of simple tachycardia and 1 of paroxysmal ventricular tachycardia (Table 1). Nineteen of the patients were in congestive heart failure. Four additional cases in the series were excluded

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because of difficulty in evaluation. They were extremely ill and all died within 5 hours after injection of ouabain. It is difficult to state whether or not the drug hastened or caused the demise of these patients. The general lack of toxic effects noted in the study makes the latter consideration unlikely. This, however, will be discussed later.

TABLE 1.—TYPES OF ARRHYTHMIAS IN VARIOUS HEART DISEASES STUDIED

Diagnosis	No. of cases	Paroxysmal auricular tachycardia	Auricular flutter	Auricular fibrillation	Simple tachycardia	Paroxysmal ventricular tachycardia	Congestive failure
Arteriosclerotic . . .	9	1	1	5	1	1	5
Hypertensive . . .	9	1	1	7	4
Arteriosclerotic and hypertensive . . .	5	..	1	4	3
Rheumatic . . .	6	6	5
Hyperthyroid . . .	1	..	1
Congenital . . .	1	1	1
No heart disease . . .	2	1	1	..	1
Total	33	2	4	24	2	1	19

According to Wyckoff and Goldring,⁷ ouabain produces an initial effect in from 5 to 20 minutes and a maximum effect in from 15 to 50 minutes when given intravenously. They found that the larger the dose, the earlier the initial effect and the more delayed the maximum effect. These authors felt that there was a definite relationship between body weight and the amount of ouabain needed to produce a therapeutic effect, just as did Eggleston³ regarding digitalis. The response to ouabain, therefore, may actually be even faster than that to strophanthin K. Speed is frequently an important consideration in view of the fact that rapid heart action, if untreated, is likely to result in congestive failure on the basis of inadequate diastolic filling of the heart. Minutes may be life-saving in value in the presence of threatening pulmonary edema or persistent cerebral anoxia. In some of the cases presented here it was definitely felt that immediate reduction of the cardiac rate was indicated. Levine and Cunningham⁵ suggested that ouabain be injected intravenously in small doses, 0.4 mg. every $\frac{1}{2}$ hour, so that there would be no danger of giving an excess of more than 0.1 mg. of the minimum toxic dose. These recommendations were based on studies in cats. Cohn and Levy² described the action of ouabain in man. They gave an initial dose of 0.1 to 0.5 mg. and a second dose of 0.3 to 0.5 mg. an hour later. Hatcher and Bailey⁴ recommended that not more than 0.5 mg. be given in 24 hours. Because of the rapid action and the rapid elimination of ouabain, Batterman, Rose and De Graff¹ outlined a method of obtaining rapid digitalization by simultaneous administration of ouabain intravenously and digitalis leaf orally.

Method. In accordance with this method, we gave 0.5 mg. (5 cat units) of ouabain* intravenously. The oral dose of digitalis leaf (4 to 8 cat units),

* The ouabain used consisted of 2 cc. ampoules, each containing 0.5 mg. or 5 cat units. The expiration date of the ampoules was individually marked. Carroll Dunham Smith Pharmaceutical Company, Orange, N. J., supplied the ouabain.

however, was usually given approximately 1 hour following the ouabain rather than simultaneously, in order to observe the effect of the ouabain *per se*. An electrocardiogram was taken in every case preceding treatment, except for several with auricular fibrillation where the diagnosis was definite clinically. The cardiac rate was determined every 5 minutes for 1 hour, then at 2 hours, 12 hours and 24 hours. ECGs were taken at varying intervals following the use of the digitalis. Digitalis was generally given in maintenance doses of 1 gr. (1 cat unit) daily, beginning approximately 24 hours after initial treatment. In no case was ouabain used if the knowledge or suspicion was present that the patient had taken digitalis during the week preceding treatment. Although symptomatic improvement (relaxation with desire to sleep, relief of bronchospasm and dyspnea, relief of palpitation and syncope) usually preceded objective evidence of improvement (sometimes within 5 minutes after injection of ouabain), a cardiac rate of 110 or less was arbitrarily selected as the time of optimum immediate effect.

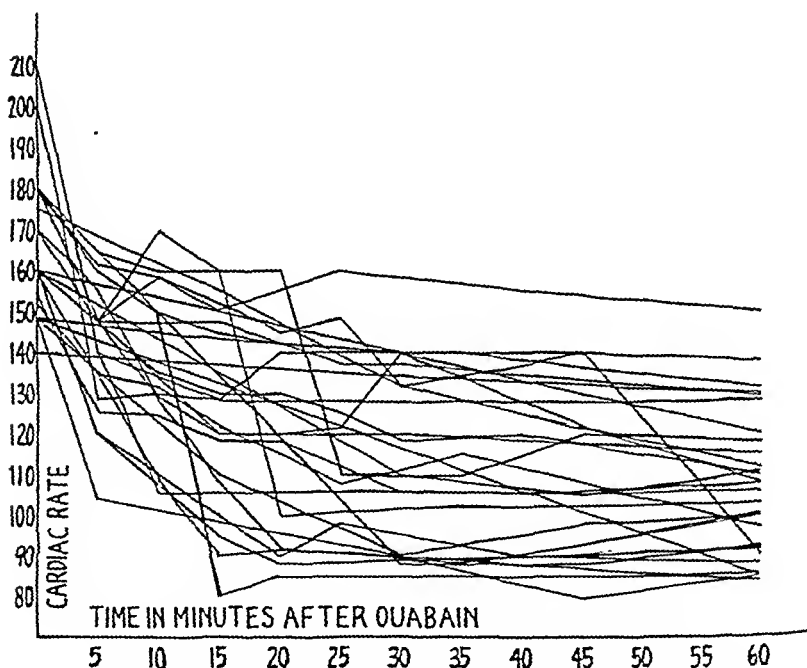


CHART 1.—Reduction in cardiac rate after ouabain treatment.

Optimum Improvement and Type of Heart Disease. Table 2 relates the optimum immediate effect to the type of heart disease. Improvement occurred in 1 hour in 4 of 9 patients with arteriosclerotic heart disease (44.4%), in 5 of 9 patients with hypertensive heart disease (55.5%), in 4 of 5 patients with arteriosclerotic hypertensive heart disease (80%), in 5 of 6 patients with rheumatic heart disease (83.3%), in 1 with thyrotoxic heart disease, not in 1 with congenital heart disease, and in neither of 2 with no heart disease. Although this study pertains to rapid arrhythmias, the findings are

consistent with those of Batterman *et al.*,¹ in which the best results were obtained in congestive heart failure associated with rheumatic heart disease. It may also be noted in Table 2 that 4 (12.1%) were improved in 10 minutes, 9 (27.3%) in 15 minutes, 10 (30.3%) in 20 minutes, 12 (36.4%) in 25 minutes, 14 (42.5%) in 30 minutes, 15 (45.5%) in 45 minutes, 19 (57.6%) in 60 minutes. Twenty-one patients (63.7%) were improved in 2 hours and 28 patients (84.9%) in 12 hours, considering all types of heart disease. Two cases (6.1%) were improved in 24 hours, and 3 patients (9.1%) were not improved after 24 hours. Two of these 3 had empyema and the third had lobar pneumonia. The latter effect was observed by Wyckoff and Goldring,⁷ who found that a greater amount of ouabain was necessary to reduce the ventricular rate in patients who had auricular fibrillation with elevation of temperature than in those without elevation of temperature.

TABLE 2.—RELATION OF OPTIMUM IMMEDIATE IMPROVEMENT* TO TYPE OF HEART DISEASE

Diagnosis	No. of cases	Time of optimum immediate improvement											
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	45 min.	1 hr.	2 hrs.	12 hrs.	24 hrs.	Over 24 hrs.
Arteriosclerotic	9		1	1		1	1	1	..	1	4		1†
Hypertensive	9		1	1		1	1	..	1	1	2		1§
Arteriosclerotic and hypertensive	5		1	1	1	..			1	..	1		
Rheumatic	6		1	1		1			2		..	1	
Hyperthyroid	1			1									
Congenital	1									1			
No heart disease	2								1†	1¶
Total	33	0	4	5	1	2	2	1	4	2	7	2	3
Per cent	100	0	12.1	15.2	3.0	6.1	6.1	3.0	12.1	6.1	21.2	6.1	9.1

* Cardiac rate of 110 or less.

† Far-advanced pulmonary tuberculosis.

‡ Lobar pneumonia.

§ Empyema.

¶ Empyema.

TABLE 3.—RELATION OF OPTIMUM IMMEDIATE IMPROVEMENT TO TYPE OF ARRHYTHMIA

Diagnosis	No. of cases	Time of optimum immediate improvement											
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	45 min.	1 hr.	2 hrs.	12 hrs.	24 hrs.	Over 24 hrs.
Paroxysmal auricular tachycardia	2			1	..	1							
Auricular flutter	4			1	1						1		
Auricular fibrillation	24		4	3		1	2		4	2	5	1	2
Simple tachycardia	2										1	1	
Paroxysmal ventricular tachycardia	1							1					
Total	33	0	4	5	1	2	2	1	4	2	7	2	3

Optimum Improvement and Type of Arrhythmia. Improvement is compared with the type of arrhythmia in Table 3. Both cases of paroxysmal auricular tachycardia were improved in 1 hour, 2 of the 4 cases of auricular flutter, 14 of the 24 cases of auricular fibrillation, the 1 case of paroxysmal ventricular tachycardia and neither of the 2 cases of simple tachycardia. These figures are difficult to interpret because of the preponderance of cases of auricular fibrillation and

the paucity of the other arrhythmias, but the results are statistically significant (determined by use of the Fisher table of t) regarding the cases of auricular flutter (50%) and those of auricular fibrillation (58.3%). The excellent response in the case of paroxysmal ventricular tachycardia is difficult to explain. The drug was given under the false assumption that it was an auricular tachycardia, but an electrocardiogram was taken a few minutes after the drug was given and revealed the nature of the arrhythmia.

TABLE 4.—RELATION OF OPTIMUM IMMEDIATE IMPROVEMENT TO AGE OF PATIENT

Age (yrs.)	No. of cases	Time of optimum immediate improvement											
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	45 min.	1 hr.	2 hrs.	12 hrs.	24 hrs.	Over 24 hrs.
10-19	1								1				
20-29	0												
30-39	3			1								2	
40-49	4		1						2				1
50-59	8			3		1				1	1		2
60-69	10		1	1		1		1	1	1	4		
70-79	6		2		1		1				2		
80-89	1						1						
Total	33		4	5	1	2	2	1	4	2	7	2	3

Optimum Improvement and Age of Patient. By inspection of Table 4, one may see that there is apparently no relationship between the rapidity of improvement and the age of the patient, the latter ranging from 19 to 82 years. Since good results occurred in the older age groups, the age of the patient is probably not a factor in considering the use of the drug.

TABLE 5.—RELATION OF OPTIMUM IMMEDIATE IMPROVEMENT TO SEX OF PATIENT

Sex	No. of cases	Time of optimum immediate improvement											
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	45 min.	1 hr.	2 hrs.	12 hrs.	24 hrs.	Over 24 hrs.
Male	18		2	4		1			1		7		3
Female	15		2	1	1	1	2	1	3	2		2	
Total	33		4	5	1	2	2	1	4	2	7	2	3

Optimum Improvement and Sex of Patient. There were 18 males and 15 females in the group studied (Table 5). In 1 hour, 8 of the 18 males (44.4%) were improved, and 11 of the 15 females (73.3%) were improved in the same period. Three of the males might be excluded because of the presence of empyema in 2 and lobar pneumonia in 1, complications which in themselves are responsible for rapid heart action. Thus, the corrected number of males improved in 1 hour is 8 of 15 patients (53.3%). In 15 minutes, however, 6 males (33.3% or 40% when corrected) and 3 females (20%) were improved. Of the 15 males, 7 (46.7%) were not improved in 1 hour, and of the 15 females, 4 (26.7%) were not improved in 1 hour. Males were more frequently improved in 15 minutes, but females were more often improved in 1 hour. These figures, however, were not subjected to statistical analysis.

Optimum Improvement and Congestive Failure. In Table 6 it may be noted that the presence of congestive failure (19 of the 33 cases) had no deterrent influence on the speed of improvement. In those with failure, 11 of 19 cases (57.9%) were improved in 1 hour, whereas in those without associated failure, 8 of 14 cases (57.1%) were improved in 1 hour.

There was no demonstrable correlation between rapidity of improvement and the initial ventricular rate.

TABLE 6.—RELATION OF OPTIMUM IMMEDIATE IMPROVEMENT TO PRESENCE OR ABSENCE OF CONGESTIVE FAILURE

Failure	No. of cases	Time of optimum immediate improvement											
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	45 min.	1 hr.	2 hrs.	12 hrs.	24 hrs.	Over 24 hrs.
Present	19	..	1	3	1	1	1	..	4	1	4	2	1
Absent	14	..	3	2	..	1	1	1	..	1	3	..	2
Total	33	..	4	5	1	2	2	1	4	2	7	2	3

Toxicity. The toxic effects noted were very few. Two of the 33 patients vomited during the observation period, but in both cases the oral dose of digitalis had been taken. The only electrocardiographic abnormalities present within 24 hours after the combination of intravenous ouabain and oral digitalis, which had not been present in the tracing prior to therapy, were inversion of the T wave in Lead I in 1 case and coupled ventricular extrasystoles in 2 cases. Other changes, such as S-T segment depression, T wave inversions, and P-R interval prolongation, occurred in other cases at varying number of days following treatment, but these changes could be related to the technique of maintaining digitalization following the initial combined method. Changes were apt to be noted if more than 1 gr. of digitalis was given daily. This study tends to corroborate the findings of Batterman *et al.*,¹ that the suggested regimen is a method of full digitalization for 24 hours, and should be followed by maintenance doses of digitalis. Wyckoff and Goldring⁷ gave 148 intravenous injections of ouabain to 32 patients with heart failure and noted no fatalities or harmful effects. They observed mild toxic symptoms in only 3 of 52 instances in which full therapeutic effects were obtained. Batterman *et al.*¹ reported that 18% of their patients showed evidence of mild toxicity at the end of 24 hours. This consisted of anorexia, nausea, vomiting or prolongation of the P-R interval. They regard this as indicating full digitalization. Cohn and Levy² found that 52% of their patients with auricular fibrillation and 12.5% of their patients with regular sinus rhythm developed ventricular premature contractions or ventricular paroxysmal tachycardia. These authors, however, gave as much as 1.1 mg. of ouabain intravenously in 2 hours.

With regard to the sudden death following the use of intravenous ouabain, it may be stated that there are many such reports with the

use of various intravenous digitalis preparations. We cannot justify the result in our 4 cases other than that they were all very critically ill. Levine and Cunningham⁵ considered that sudden death following intravenous injection of digitalis might be avoided by their fractional administration technique. This plan is especially valuable, as they themselves admit, if the patient has already received digitalis. We utilized this suggestion satisfactorily in 1 of our cases suspected of having had some digitalis prior to ouabain administration by giving a "test dose" of 0.1 mg. (1 cat unit).

Return to Normal Rhythm. Normal rhythm returned within 48 hours of treatment in 7 of the 24 cases of auricular fibrillation and in other cases of auricular fibrillation at longer intervals.

Summary. 1. A study was made of 33 cases of rapid cardiac arrhythmias, consisting of 2 cases of paroxysmal auricular tachycardia, 4 of auricular flutter, 24 of auricular fibrillation, 2 of simple tachycardia and 1 of paroxysmal ventricular tachycardia.

2. Ouabain produced an optimum immediate effect (sustained ventricular rate of 110 or less) in 1 hour in 44.4 to 83.3% of all heart disease cases except in the 1 case of congenital heart disease and in the 2 cases without heart disease. Nineteen patients (57.6%) were improved in 1 hour, 21 (63.7%) in 2 hours and 28 (84.9%) in 12 hours. These figures are statistically significant.

3. Optimum immediate improvement occurred in 1 hour in both cases of auricular tachycardia, in 2 of 4 cases of auricular flutter (50%), in 14 of the 24 cases of auricular fibrillation (58.3%), in the 1 case of ventricular tachycardia, and in neither of the 2 cases of simple tachycardia. The figures for flutter and fibrillation have statistical significance.

4. There was no correlation between optimum improvement and age of the patient, associated congestive failure, or initial ventricular rate. Females were more often improved in 1 hour (73.3%) than males (53.3%), but males were more often improved in 15 minutes (40%) than females (20%). The significance of the difference between the sexes was not determined.

5. Toxic effects (vomiting, T wave inversion in Lead 1 and coupled ventricular extrasystoles) noted were very few.

6. Normal rhythm returned in 7 of the 24 cases of auricular fibrillation within 48 hours.

7. The total absence of syphilis for a series in a hospital where approximately 15% of the cases of heart disease have syphilitic etiology emphasizes the rarity of underlying luetic heart disease in rapid cardiac arrhythmias.

Conclusions. 1. One intravenous dose of ouabain produces a statistically significant reduction in ventricular rate and is an effective method of treating rapid cardiac arrhythmias of auricular origin. It is relatively ineffective when the mechanism is that of a simple tachycardia or when complicated by severe infection.

2. When combined with 1 oral dose of digitalis, intravenous ouabain is an effective aid in producing full digitalization.

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THE COMPARATIVE VALUE OF HIGH AND LOW DOSES OF SULFADIAZINE IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA

BY HARRY F. DOWLING, M.D.

CLARENCE R. HARTMAN, M.D.

WASHINGTON, D. C.

HARRY A. FELDMAN, M.D.

FORT MC PHERSON, GA.

AND

FRANK A. JENKINS, M.D.

FORT GEORGE G. MEADE, MD.

(From the Health Department, The District of Columbia, The Department of Medicine, George Washington University, and the Gallinger Municipal Hospital)

SEVERAL of the sulfonamide drugs have been used effectively in the treatment of pneumococcus pneumonia since 1938.⁵ The compounds which have been most extensively and successfully used for this purpose, sulfapyridine, sulfathiazole and sulfadiazine, have been studied thoroughly with regard to their absorption and excretion, their therapeutic effects in pneumonia and other diseases, and their toxic reactions. On the other hand, the relation of the dosage of these drugs to the outcome of the disease has not been given much attention. Evans and Gaisford⁵ used an initial dose of 2 gm. by mouth in adults, followed by 1 gm. every 4 hours. In this country, doses of all 3 drugs have varied from 2 to 6 gm. initially, usually followed by 1 gm. every 4 hours.¹ Garvin¹⁰ employed 4 gm. of sulfathiazole or sulfapyridine initially, with subsequent doses of 2 gm. every 4 hours until improvement occurred, when the dose was lowered to 1 gm. every 4 hours. Billings and Wood² used 0.1 gm. of sodium sulfadiazine per kg. of body weight, intravenously, as an initial dose, followed by 1 gm. of sulfadiazine by mouth every 4 hours with the object of attaining high blood levels early in the course of treatment.

In order to determine the effect of relatively high doses of the sulfonamides, as compared with low doses, in the treatment of pneumococcus pneumonia, we conducted a study as follows: Sputum for typing and blood for culture were collected immediately on all patients admitted to the medical wards of the Gallinger Municipal Hospital who were suspected of having pneumonia. Following these procedures, the patients on the 4 adult wards, comprising the Georgetown Medical Division* were given an initial dose of 6 gm. of sulfadiazine orally, followed by 1 gm. every 4 hours. (For the sake of brevity, we have called this the high dose.) Patients on the 4 adult medical wards of the George Washington Medical Division* were given 2 gm. statim and 0.5 gm. every 4 hours thereafter (which we have called the low dose). Patients were referred alternately to these divisions by a central admitting office. The drug was continued in all cases until the temperature had been normal for 3 or 4 days and the clinical condition improved, when therapy was discontinued abruptly. Whenever a patient failed to improve, specific antipneumococcic serum was administered, while the dosage of sulfadiazine was held constant. Specific serum was considered necessary in only 5 cases. Three of these patients had received the low doses of sulfadiazine. Two of them died and 1 recovered promptly after administration of the serum. Both of the patients in the high-dosage series who received serum died.

TABLE 1.—RESULTS OF TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH DIFFERENT DOSES OF SULFADIAZINE

Time before temperature dropped below 101° F. (hours)	Low dose			High dose		
	All cases	Bacteremic cases	%	All cases	Bacteremic cases	%
Under 23	31 (38.3%)	2	59 3	36 (45.6%)	5	68 4
24- 47	17	3		18	2	
48- 71	9	0		1	0	
72- 95	4	1		6	0	
96-119	3	0	24 7	1	1	12 7
120 and over	4	1		2	0	
Excluded because tempera- ture already down when drug begun	8	1	9 9	7	0	8 8
Died	5	1	6 2	8	5	10 1
Total	81	9	100	79	13	100
% bacteremic	—	11 1	—	—	16 5	—

In evaluating the results, only typed cases of pneumococcic pneumonia with unequivocal clinical and roentgenographic evidence of the disease have been considered. As shown in Table 1, 81 patients with pneumococcic pneumonia were given the low dose of 2 gm. followed by 0.5 gm. every 4 hours, and 79 the high dose of 6 gm. followed by 1 gm. every 4 hours. It will be seen that there is no

* We wish to thank the Attending and Resident Staffs of the two divisions for their whole-hearted cooperation.

striking difference in the outcome in the 2 groups. There was a slight tendency for the temperature to fall sooner in the patients treated with the higher doses, since 36 patients (45.6%) of this group showed a permanent drop in temperature to below 101° F. by mouth within 24 hours, as compared with 31 patients (38.3%) among those treated with the lower doses. Within the first 48 hours the temperature of 54 (68.4%) of the patients receiving higher doses had fallen below 101° F., as compared with 48 (59.3%) of those in the lower-dose group. Only 10 patients (12.7%) who recovered after receiving the higher doses experienced a fall in temperature below 101° F. later than 48 hours after the commencement of therapy, whereas 20 patients (24.7%) of those who recovered after receiving the lower doses of sulfadiazine took longer than 48 hours to reach a point below 101° F. There were 5 deaths in the low-dosage group and 8 among the patients receiving higher doses. However, several of these deaths could be attributed in great part to complicating diseases. Among the patients who died in the low-dosage group, 1 patient had far-advanced bronchiectasis and another committed suicide during the course of the pneumonia. Among patients who died in the higher-dosage group, 1 patient had hypertensive heart disease, 1 had chronic glomerulonephritis, and 2 were suffering from acute and chronic alcoholism. If the patients with complicating diseases are omitted from consideration, there would remain 3 deaths in the low-dosage series as against 4 in the high-dosage series. There is another important factor to be compared in the 2 groups. The incidence of bacteremia was greater in the higher-dosage series (13 cases—16.5%) than in the low-dosage series, where there were only 9 cases (11.1%).

An indirect method of measuring the rapidity of improvement is by determining the average number of days spent in the hospital by the surviving patients in each group. This was done for the patients under consideration, only those being excluded who had empyema or who had other diseases than the pneumonia which would have increased their length of stay. The average number of days in the hospital was 16.1 for the low-dosage group and 12.7 for the high-dosage group, a difference of 3.4 days.

Table 2 shows the incidence of complications in the two groups. Slow resolution of the pneumonic consolidation was observed in 9 patients who received low doses of sulfadiazine and in 4 patients who were given the higher doses. Slow resolution was characterized by the presence of dullness, abnormal breath sounds and voice sounds and râles, plus Roentgen ray evidence of consolidation, often accompanied by low-grade fever, persisting for a period of 3 weeks or more after the symptoms of the acute illness were over. A relapse of the pneumonia, or a spread to another lobe, or both, occurred in 3 patients receiving low doses of sulfadiazine. One patient in the group who received high doses suffered from a relapse.

TABLE 2.—INCIDENCE OF COMPLICATIONS IN PATIENTS WITH PNEUMOCOCCIC PNEUMONIA TREATED WITH DIFFERENT DOSES OF SULFADIAZINE

Complication	Low dose		High dose	
	All cases	Bacteremic cases	All cases	Bacteremic cases
Delayed resolution . . .	9	3	4	1
Relapse and/or spread . .	3	1	1	0
Empyema*	1	0	1	0
Endocarditis*	0	0	1	1

* Not present on admission.

Toxic reactions from sulfadiazine were infrequent in all the patients treated, as is shown in Table 3. One patient in each group had fever caused by the drug. Four patients in the low-dosage group suffered from a psychosis which was apparently due to the sulfadiazine, as compared to 2 patients with psychosis in the high-dosage group. One patient in the low-dosage group developed a drug dermatitis, while gross hematuria, presumably from a renal calculus, and a leukemoid reaction, were each present in 1 patient in the high-dosage group. All of the patients with toxic reactions to the sulfadiazine recovered without sequelæ.

TABLE 3.—TOXIC REACTIONS IN PATIENTS RECEIVING HIGH AND LOW DOSES OF SULFADIAZINE

Toxic reaction	Low dose	High dose	Both groups
Drug fever	1	1	2
Drug psychosis	4	2	6
Hematuria	0	1	1
Drug dermatitis	1	0	1
Leukemoid reaction	0	1	1
Total	6	5	11

Determinations of free blood sulfadiazine were usually made 6 hours after the first dose was administered and every morning thereafter as long as sulfadiazine was being given. There was no close parallel between the dose of the drug and the blood sulfadiazine levels, although in general the patients receiving the higher doses tended to have higher blood levels. The average free blood sulfadiazine at 6 hours after the first dose of 2 gm. in 22 patients given low doses was 3.2 mg. per 100 cc., as compared to 4.9 mg. per 100 cc. among 16 patients in the high-dosage series. Once the free blood sulfadiazine level was established in a given patient, it remained fairly constant, usually within 2 mg. per 100 cc. The lowest average daily blood level for any patient in the low-dosage group was 2.4 mg. per 100 cc., and in the high-dosage group 4.5 mg. per 100 cc. The median average daily blood levels for the two groups were 5.25 and 7.55 mg. per 100 cc. respectively, while the highest average daily blood levels for the corresponding groups were 11.8 and 13 mg. per 100 cc.

Discussion. No accurate method is available to us for measuring the various degrees of effectiveness which a given therapeutic agent

may have in an infectious disease. The occurrence of recovery or death is a very crude measurement, since it is affected by many extraneous factors. In the present series, no significant differences can be found in the death rates in the group of patients treated with low doses of sulfadiazine as compared with those given high doses, when allowance is made for the presence of bacteremia and of unrelated, complicating diseases. Accordingly, we have compared the two groups with respect to the following factors: (1) the time required for the temperature permanently to reach a level below 101° F., (2) the average length of stay in the hospital and (3) the incidence of complications of the pneumonia which developed after admission to the hospital.

The fall in temperature is influenced by many other factors than the therapeutic agent used. The temperature in cases of pneumococcus pneumonia sometimes falls without specific treatment as early as the first or second day of the disease. In some patients it may never reach a high level. In other patients the temperature may be depressed or elevated as the case might be by the presence of other infections, by poor circulation, by chilling, by the use of antipyretic drugs or by metabolic factors, and so on. Furthermore, there is no definite point in the temperature curve which indicates that recovery has taken place. We have arbitrarily chosen 101° F. as a dividing line, because the temperature incident to resolution alone seldom goes as high as this. In view of all these possible variables, and since the blood levels obtained with the high doses were often no higher, and sometimes even lower, than those obtained with the low doses, we feel that the slightly greater percentage of cases in which the temperature fell below 101° F. within 48 hours after the beginning of treatment in the higher-dose series (68.4%) than in the low-dose series (59.3%) may be significant. This is made more likely by the fact that the length of stay in the hospital was 3.4 days greater in the low-dose than in the higher-dose group.

Although the serious complications of the pneumonias were too few in number for comparison, the less serious complications, delayed resolution and relapse, were found to be more than twice as frequent among the low-dosage patients as among those receiving the higher doses. Since all of these results point in the same direction, it seems reasonable to conclude that, whereas no benefit in mortality rate is to be expected from the use of an initial dose of 6 gm. of sulfadiazine followed by 1 gm. every 4 hours in the adult with pneumococcus pneumonia, as compared with an initial dose of 2 gm. followed by 0.5 gm. every 4 hours, nevertheless the higher doses are more often followed by rapid recovery than the lower doses, and that there is less likelihood of relapse or spread of the pneumonia to another lobe, or of delayed resolution in the patients receiving the higher doses.

Furthermore there seems to be no deleterious effect from the use of the higher doses. In our series the incidence of toxic symptoms from the sulfadiazine was practically the same in each group. This is in contrast to the findings of Detweiler and his associates,³ who observed the more frequent occurrence of hematuria, oliguria, anuria, leukopenia, rashes and fever, when high doses of sulfapyridine (as much as 2 gm. every 4 hours) were given than when low doses were administered. The different results obtained by us are attributable partly to the fact that sulfadiazine causes fewer toxic reactions than the other sulfonamide drugs,^{4,7,9} and partly to the fact that we did not employ at any time doses in excess of 1 gm. every 4 hours.

In the present study we have been concerned with determining, by means of controlled case studies, whether there is any great advantage to be derived from the use of high doses of sulfadiazine as compared with lower doses. The evidence seems to point conclusively to the fact that the routine employment of higher doses offers no such advantage. On the other hand, there seems to be no disadvantage from the use of the comparatively higher doses as usually administered and they should certainly be used in patients suffering from pneumonia with uncertain or poor prognosis. Most of the factors which often indicate a poor prognosis in pneumonia are known: age over 40 years, involvement of more than one lobe, infection with the Type III pneumococcus, bacteremia, or the presence of pregnancy or another complicating disease. If any of these factors are present, a high dose of sulfadiazine, preferably 6 gm. in an adult, should be given at the onset, followed by 1 gm. doses at 4-hour intervals. The initial dose might even be given intravenously as suggested by Billings and Wood,² or subcutaneously, especially in poorly hydrated patients.

Sulfadiazine concentrations in the body, like those of the other sulfonamides vary directly with the degree of absorption from the intestines and inversely with the amount of acetylation and the speed of excretion. Consequently the level at which sulfadiazine will be maintained in the blood of a given individual by a certain dosage of the drug is predictable only within broad limits. In every case in which the drug is administered, we recommend that the free blood sulfadiazine level be determined within 12 to 24 hours of the beginning of treatment and further doses adjusted accordingly. Patients who are markedly dehydrated at the time of admission, or who have evidences of primary renal disease, or who are in congestive heart failure of any degree should have their blood levels determined at least once per day, since these patients are subject to rapid accumulations of the sulfonamide drugs.

In view of the fact that the production of sulfonamides is still limited and that isolated military groups may upon occasion have inadequate supplies of these drugs on hand, we merely wish to point out that under those circumstances patients with pneumococci

pneumonia may be treated with smaller doses than are usually recommended without apparently increasing the mortality rate.

Summary and Conclusions. 1. Eighty-one unselected adults with typed pneumococcic pneumonia were treated with an initial dose of 2 gm. of sulfadiazine followed by 0.5 gm. every 4 hours until recovery was certain or death ensued; while an alternate group of 79 patients was given 6 gm. initially, followed by 1 gm. every 4 hours.

2. There was no significant difference in mortality in the two groups, nor in the incidence of serious complications of the pneumonias.

3. In the patients receiving the higher doses of sulfadiazine, there was a slight tendency for the temperature to fall more rapidly than in the low-dose group; the duration of the hospital stay of the patients averaged 3.4 days less for the high-dose group; and the incidence of relapse, spread of the pneumonia to another lobe and slow resolution was less than half as much in the high-dosage group as in the low-dosage group.

4. Toxic reactions from sulfadiazine were infrequent in both groups, and no more numerous in the high-dosage than in the low-dosage group.

5. It is concluded that, whereas higher doses of sulfadiazine are slightly more often followed by rapid recovery than the lower doses and that there is less likelihood of relapse, spread of the pneumonia to another lobe, or of delayed resolution in the patients receiving the higher doses, nevertheless definitely smaller doses of the drug than are usually recommended can be used without fear of an increase in the mortality rate or of serious complications. This is significant in view of the fact that in the present emergency limitations of the supply of the sulfonamides may occur at times.

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THE VASODILATING EFFECTS OF NICOTINIC ACID

(RELATION TO METABOLIC RATE AND BODY TEMPERATURE)

BY GRACE A. GOLDSMITH, M.D.

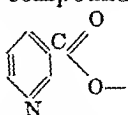
ASSISTANT PROFESSOR OF MEDICINE, TULANE UNIVERSITY; VISITING PHYSICIAN,
CHARITY HOSPITAL OF LOUISIANA

AND

SHIRLEY CORDILL, B.A.

(From the Department of Medicine, School of Medicine, Tulane University of
Louisiana and the Charity Hospital of Louisiana)

NICOTINIC acid administered orally or intravenously in sufficient dosage causes flushing and burning of the skin, especially of the face and neck, and at times, of the entire body. This vasodilator response was first described in 1937 and 1938 by several groups of investigators.^{3,5,7} Bean and Spies² in 1940 studied a number of pyridine compounds and found that only those containing the free

radical  produced vasodilatation. They suggested that

the reaction takes place in the arterioles of the skin as it is abolished by adrenalin, and postulated that it might be due to the liberation of histamine. Abramson, Katzenstein and Senior,¹ using a plethysmographic method, found that nicotinic acid caused a significant increase in the blood flow in the hand and forearm and a slight increase in the leg. They concluded that, as the blood pressure and pulse rate were not consistently altered, the peripheral vascular effects were due to local changes in the blood-vessels rather than to an increase in cardiac output.

This investigation was undertaken in an endeavor to elucidate further the mechanism responsible for the vasodilatation produced by nicotinic acid. The vasodilator response could be compensatory to an increase in heat production, or it might be due to central vasomotor stimulation, or to peripheral action either on nerve ending or directly on the blood-vessels.

In order to determine whether or not the skin reaction was due to an increase in heat production, the effect of nicotinic acid on metabolic rate and on body temperature was investigated. Unna,⁸ studying the effect of nicotinic acid on the metabolism of rats, found no change in oxygen uptake. Spies, Bean and Stone⁶ reported that nicotinic acid given to 7 normal subjects caused no uniform variation in oxygen consumption during the period of flushing.

In the present study, the metabolic rate was measured in 8 normal subjects on 17 occasions using the Benedict-Roth apparatus. After several determinations in the basal state, 50 to 200 mg. of

nicotinic acid* were given orally with 30 to 60 cc. of water and the metabolic rate measured at intervals. Some tests were begun as early as 4 minutes and some as late as 44 minutes after administration of nicotinic acid. On a few occasions 30 to 60 cc. of water alone were given to determine whether or not this amount of liquid in the stomach would influence metabolism. The findings are given in Table 1. There was no appreciable change in metabolic rate after nicotinic acid had been ingested, even when a severe vasodilator response ensued. This was true regardless of whether the rate was determined before the skin reaction occurred, or at its height. In a few subjects there was a slight increase in metabolic rate when the vasodilating effects of nicotinic acid were experienced for the first time. Discomfort and anxiety presumably explain this elevation since no rise occurred in subsequent tests on the same subject even when flushing was more intense. There was no significant change in blood pressure or pulse rate, except in 1 subject who had mild hypertension, in whom both the systolic and diastolic blood pressures increased 15 to 20 mm. of mercury during each experiment. On one occasion, however, there was a rise in blood pressure before nicotinic acid was given.

The skin reaction, which was noted 4 to 23 minutes after the ingestion of nicotinic acid, began with a sensation of tingling in the fingers followed by tingling, burning, or a "starched" feeling in the face, especially in the forehead, across the bridge of the nose, in the cheeks and ears. One or more minutes after the burning appeared the skin over the face, ears and back of the neck became flushed. In some instances there was injection of the conjunctivæ and circumoral pallor. When the reaction was intense, the flush spread from the face to the neck, extending down to about a V neck-line in front, and spreading between the scapulæ posteriorly and over the tips of the shoulders. The flush was a mottled red rather than a smooth diffuse color. If the arms were involved redness appeared first in the antecubital fossa, later on the extensor surfaces of the arm and forearm, and rarely on the palms of the hands or flexor aspects of the arm and forearm. Burning and redness were often present in the region of the sacrum and in the perineum. The anterior surface of the thighs and knees became flushed in a few instances, and 1 subject had an area of vasodilatation around the anterior surface of the ankle. Other areas of the lower extremities and trunk were rarely involved.

The height of the flush was reached 4 to 20 minutes after its appearance and lasted from 10 minutes to 1½ hours. A few individuals had a secondary reaction after the first had faded, or when they got up and moved about after completion of the metabolic tests. In 2 subjects the vasodilatation appeared and disappeared several times. In a few experiments a generalized urticarial rash

* The nicotinic acid was furnished through the courtesy of Merck & Co.

developed as the redness faded. The only toxic effects noted were vomiting in 1 subject, substernal distress in another and a sensation of severe pressure in the ears in a third.

TABLE 1.—THE EFFECT OF NICOTINIC ACID ON THE METABOLIC RATE IN RELATION TO THE SKIN REACTION

Subject	Basal metabolic rate	Amount nicotinic acid given (mg)	Metabolic rate after nicotinic acid		Skin reaction		
			Time (min)	Rate	Time of onset (min)	Time of maximum flush (min)	Severity
E	-13	100	8	-12	4	8	Mild
	-16		19	-15	30*		Moderate
E	-15†	100	6	-14	3	14	
	-15		20	-11			Moderate
	-11						
G	+18	50	5	+16	11	15	Severe
	+6		15	+16			
S	-10	50	4	-4	5	17	Severe
	-3		23	+3			
S	+1	100	6	+2	7	20	Severe
	-1		20	+2			
S	0	100	5	0			None
	0		31	+2			
L	-16	100	6	-3	9	19	Severe
	-19		21	-19			
			44	-19			
L	-20	100	6	-19	14	20	Mild
	-19						
	-19†		19	-18			
L	-16	200	6	-19	14	32	Mild
			21	-16			
			34	-19			
K	-14	50	6	-14			None
	-14	50	10	-14	12	22	Mild
K	-19	100	6	-16	7	16	Mild
	-15		18	-16			
C	-3	100	6	-3	10	18	Moderate
	-13†		12	-7			
	-8		29	-13			
C	-7	100	6	+1			Moderate
	-7		20	-7	7	10	
C	-9	150	6	-6	6	17	Moderate
	-14		17	-14			
T	-23	100	6	-18	23	30	Moderate
	-20		21	-19			
T	-18	200	6	-16	6	25	Severe
	-21		16	-23			
			33	-26			
			39	-23			
O	-26	200	20	-22	8	12	Severe
	-19						

* A secondary flush occurred.

† 60 cc of water had been administered

The effect of nicotinic acid on body temperature was studied in a number of experiments. In 11 patients the rectal temperature was recorded prior to and at 5-minute intervals after the administration of 100 to 200 mg. of nicotinic acid, for periods of 40 to 60 minutes. In 8 of the 11 tests a typical vasomotor response occurred 5 to 20 minutes after nicotinic acid was given. Before the appearance of vasodilatation there was a rise of temperature of 0.4° and 0.6° F. in 2 instances; a fall of temperature of 0.2° , 0.4° and 1° F. in 3 instances, and no change in 3 additional tests. In each of 3 subjects who had no vasodilator response to nicotinic acid, there was a rise in temperature of 0.2° F. during similar time intervals. In the subject who showed a fall in temperature of 1° F. the flush appeared concomitant with the temperature change. One subject whose vasodilator response was severe and of long duration had a fall in oral temperature of 2° F. at the end of 90 minutes. Shivering occurred at this time. All of the above studies were conducted in the warm environment of a hospital ward.

Five experiments were performed at 68° to 71.5° F. in a constant-temperature room. Oral temperatures only were recorded. In no instance was there a rise in body temperature after giving 50 to 100 mg. of nicotinic acid. In 3 instances the nicotinic acid caused marked vasodilatation, which was followed by a drop in temperature of 0.8° , 0.4° and 0.8° F. Such a fall was not observed after comparable periods of time when no vasomotor reaction occurred or when no nicotinic acid was administered. In the same subjects no fall in temperature occurred in a warm environment.

Two experiments* were performed in a room of constant temperature, using a rectal thermocouple sensitive to changes of 0.003° C. There was a slight rise in temperature before vasomotor changes appeared in one experiment and no change in a second test after 200 mg. of nicotinic acid were given orally. After vasodilatation had occurred, there was a significant fall in temperature in both experiments.

A number of observations made at various environmental temperatures yielded interesting findings which may have a bearing on the mechanism by which nicotinic acid causes a skin reaction. In tests on 1 subject it required a larger amount of nicotinic acid to produce a vasomotor response at a room temperature of 68° to 70° F. than at one of 82° F. or higher. Fifty milligrams were usually sufficient to cause marked vasodilatation in a warm environment whereas 100 mg. often failed in a cold one. In several experiments at a room temperature of 68° F. a lamp was placed over one area of the body, either (1) the antecubital fossa, (2) the ear and side of the face, or (3) the knee, and 100 mg. of nicotinic acid was given. A slight vasodilatation was produced in the areas which had been warmed, while other areas were unchanged. This flush

* These studies were made through the courtesy and coöperation of Dr. Roy Turner.

had the splotchy appearance of that induced by nicotinic acid and did not occur with heat alone when no nicotinic acid was given. A marked and generalized reaction was induced in a cold environment on one occasion when first one and then the other side of the face was warmed. This reaction occurred 40 minutes after giving nicotinic acid which is much later than the usual time of response (4 to 20 minutes). These findings could be interpreted in several ways. The heat may merely have aided the nicotinic acid in overcoming the vasoconstriction due to the cold, or the increased blood supply to the area induced by the heat may have allowed a sufficient concentration of nicotinic acid to develop in the part to cause a local reaction of vasodilatation.

As mentioned previously, some subjects who ingested nicotinic acid to determine its effect on oxygen consumption, developed a secondary flush when they got up and moved about. The changes in circulation resulting from exercise may have increased the concentration of nicotinic acid in the periphery with resultant local vasodilatation and a second skin reaction.

The vasodilatation produced by nicotinic acid does not appear to be due to stimulation of the parasympathetic nerves. Loman, Rinkel and Myerson⁴ reported that nicotinic acid is not synergistic with prostigmine nor is its action antagonized by atropine. In a few experiments we found that neither atropine nor prostigmine had an appreciable influence on the vasodilator response to nicotinic acid. Spies has stated that there is an antagonism between adrenalin and nicotinic acid. In a few tests we found that the administration of adrenalin could either prevent the flush produced by nicotinic acid, or cause its disappearance if given at the height of the reaction. When only a small quantity of adrenalin was used, the peripheral vasoconstriction was of short duration, and the typical flush of nicotinic acid reappeared after a few minutes.

Conclusion. The administration of nicotinic acid produced no significant change in metabolic rate or body temperature before the appearance of the characteristic skin reaction. The vasodilatation, therefore, does not seem to be compensatory to increased heat production. Available evidence at the present time suggests that the vasodilator response is due to a local effect on the arterioles in the skin.

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RELATIONSHIP OF NIACIN (NICOTINIC ACID) TO PORPHYRINURIA IN THE AGED*

BY HENRY A. RAFSKY, M.D., F.A.C.P.

AND

BERNARD NEWMAN, B.S., CH.E.

NEW YORK, N. Y.

(From the Hospital and Home of the Daughters of Jacob)

IN a previous article⁹ we reported the fact that porphyrinuria was a comparatively frequent finding in so-called normal aged individuals. As the usual causes of porphyrinuria were not present in these subjects, it was thought of interest to give them varying amounts of niacin (nicotinic acid) to note the effect, if any, on the increased excretion of ether-soluble red pigments.

Experimental Study. Altogether 55 subjects were studied. Twenty-six were males, and 29 females. Their ages ranged from 63 to 91 years. All were ambulatory, were housed in the "Home" division of the institution, and were on the normal institutional diet. Daily, at 11 A.M., 50 mg. of niacin were given by mouth. The urine was collected at 6 A.M. the following day, and was then examined for porphyrins. This was done on each successive day, until the urine no longer gave a positive test result for porphyrins. The method used in detecting the porphyrinuria was that described by Beekh, Ellinger and Spies.¹ The urine was considered porphyrin-free if negative test results were obtained on 2 successive days. Our findings are outlined in Table 1.

TABLE 1.—AMOUNT OF NIACIN NECESSARY FOR DISAPPEARANCE OF PORPHYRINURIA

Niacin (mg.)	No. of subjects
100	1
150	3
200	2
250	5
300	2
350	6
400	5
450	11
500	4
550	4
600	3
650	3
700	1
750	3
800	2

The storage of niacin during these studies was also investigated as follows: As soon as the urine became porphyrin-free, the administration of niacin was discontinued, and the urine was examined daily to see if a positive test result was again obtained. The findings were considered to be positive if porphyrinuria was observed on 2 successive days (see Table 2).

* The niacin (nicotinic acid) and other vitamin products used were supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, N. J.

TABLE 2.—LENGTH OF TIME THAT ADMINISTERED NIACIN WAS STORED AS EVIDENCED BY RETURN OF PORPHYRINURIA

Days	No. of subjects
1	1
2	2
3	7
4	16
5	6
6	9
7	5
8	8
9	1

The amounts of niacin necessary to check the urinary excretion of ether-soluble red pigments of those subjects who were found to have had urinary porphyrins, before treatment, ranged from 100 mg. to 800 mg., with an average value of 475 mg. In every instance in which porphyrinuria was encountered, the administration of niacin corrected this condition. The length of time that the administered niacin was stored in the body, as evidenced by the time required for the reappearance of porphyrinuria, ranged from 1 to 9 days, with an average of 5 days.

To check on the quantitative excretion of niacin in patients showing increased porphyrinuria, 24 hour urinary niacin excretions were determined for 3 patients who showed a positive porphyrin test result and who were given 50 mg. of niacin daily; and on 4 patients who showed no porphyrinuria and who were given no niacin. The procedure employed for the determination of the niacin in the urine was that described by Rosenblum and Jolliffe.¹³ These observers considered 3.4 to 10.2 mg. of niacin to be the normal daily excretion in young healthy adults. Melnick, Robinson and Field⁷ reported that for 11 adults, whose ages were not given, the daily excretion of niacin was found to be from 1.7 to 29.3 mg. Perlzweig, Levy and Sarett⁸ found the daily excretion to be from 2.5 to 19.4 mg. in patients, ranging in age from 19 to 49 years, who had ingested 100 or 200 mg. doses of niacin. Seven of our subjects, 3 of whom showed evidence of porphyrinuria, received from 0 to 300 mg. of niacin. The daily excretion of the latter ranged from 6.8 to 11.1 mg. (Table 3). The amount of niacin excreted by our subjects remained at approximately the same level, whether the patient showed a porphyrinuria or not.

TABLE 3.—DAILY EXCRETION OF NIACIN IN PATIENTS WITH AND WITHOUT PORPHYRINURIA

No.	Patient	Sex	Age	Porphyri- nuria	Niacin	
					Amount ingested (mg.)	Daily excretion, (mg.)
1	A. B.	M	80	+	0	6.8
2	H. G.	M	74	—	0	8.0
3	S. H.	M	76	+	300	11.1
4	I. R.	M	79	+	300	7.9
5	A. C.	F	81	—	0	8.1
6	R. A.	F	79	—	0	7.0
7	R. K.	F	78	—	100	10.0

In order to establish the fact that niacin alone was responsible for the disappearance of the porphyrinuria, daily porphyrin determinations were made on the urine of individuals who showed a positive result and who were not given any niacin. This was also done for those individuals who showed no increased porphyrin excretion. In no individual showing por-

pyrinuria in this control series, did the increased excretion of ether-soluble red pigments disappear on 2 successive days without the administrations of niacin. The results obtained in this control series are outlined in Table 4. As a further control, varying amounts of ascorbic acid were given to 7 subjects who showed a positive reaction for porphyrinuria. An initial dose of 100 mg. of ascorbic acid was given by mouth to each of these individuals. This dosage was gradually increased until the subjects were given 1000 mg. of ascorbic acid at one time. The increased dosages were administered at intervals far enough apart to insure complete excretion of the previous one. Determinations were made of the urinary excretion of ascorbic acid in all the subjects and the plasma level of ascorbic acid in most of them, and also of the presence or absence of ether-soluble red pigments. It was observed that the excretion of porphyrin bodies did not

TABLE 4.—DAILY DETERMINATIONS OF URINARY PORPHYRINS (CONTROLS)

No.	Patient	Sex	Age	Porphyrin test result										
				Days										
				1	2	3	4	5	6	7	8	9	10	11
1	A. S.	M	83	+	+	+	+	—	+	+	+	—	+	+
2	L. G.	F	71	+	+	—	+	+	+	+	+	+	+	+
3	P. C.	F	78	—	—	—	—	—	—	—	—	—	—	—
4	A. R.	F	75	—	+	—	—	—	—	+	—	—	—	—
5	P. C.	M	82	+	+	+	+	+	+	+	+	+	+	+
6	H. S.	M	76	—	—	—	+	—	—	—	—	—	—	—

TABLE 5.—EFFECT OF ASCORBIC ACID IN VARYING AMOUNTS

Subject																
S. B. Age, 83 Sex, F		M. S. Age, 70 Sex, F		E. S. Age, 80 Sex, F		E. S. Age, 89 Sex, F		B. B. Age, 74 Sex, M		M. F. Age, 71 Sex, M		S. S. Age, 84 Sex, M		P. C. Age, 76 Sex, M		
Vita- min		Vita- min		Vita- min		Vita- min		Vita- min		Vita- min		Vita- min		Vita- min		
Dosage (mg.)	Por.	C	Por.	C	Por.	C	Por.	C	Por.	C	Por.	C	Por.	C	Por.	C
100 . .	+	22 ¹	+	11 ²	+	30 ³	+	19 ⁴	+	20 ⁵	+	10 ⁶	+	18 ⁷	+	9 ⁸
200 . .	+	83	+	26	+	63	+	21	+	27	+	21	+	10	+	10
300 . .	+	87 ⁹	+	56					+	33 ¹⁰						
400 . .	—	9	+	108 ¹¹	+	100 ¹²	+	52			+	29	+		+	18
500 . .	+	117	+	110			+	60 ¹³	+	100						
600 . .	+		+	260	+	380			+		+	115			—	55 ¹⁴
700 . .	+	230	+	318			+	91	+	180			+	125 ¹⁵	+	100
800 . .	+	250			+	420			+	190	+	200 ¹⁶				
900 . .							+	116 ¹⁷					+	212	+	212 ¹⁸
1000 . .			+	780 ¹⁹			+	270	+	415 ²⁰	+	430 ²¹			+	320

+ denotes a positive test for ether-soluble red pigments.

— denotes a negative test for ether-soluble red pigments.

Ascorbic acid excretions are given in milligrams *per diem*.

Plasma values of ascorbic acid (superior figures) mg. per 100 cc. of plasma:

1, 0.58; 2, 0.62; 3, 0.60; 4, 0.40; 5, 0.92; 6, 0.30; 7, 0.42; 8, 0.54; 9, 0.80; 10, 0.91; 11, 0.88; 12, 0.67; 13, 0.58; 14, 0.73; 15, 0.80; 16, 1.08; 17, 0.90; 18, 0.95; 19, 1.20; 20, 2.16; 21, 2.64.

TABLE 6.—EFFECT OF SYNTHETIC NIACIN-FREE B COMPLEX ON PORPHYRINURIA

Subject	Age	Sex	Porphyrinuria test						
			Days						
			1	2	3	4	5	6	7
Y. E.	87	F	+	+	+	+	+	+	+
P. A.	79	F	+	+	+	+	+	—	+
P. L.	88	F	+	+	+	+	+	+	+
P. C.	69	M	+	+	+	—	+	+	+
C. N.	84	M	+	+	—	+	+	+	+
C. S.	76	M	+	+	+	+	+	+	+
F. W.	83	F	+	+	+	+	—	+	+

change for 2 successive days in any of these individuals, the high ascorbic acid retention and elevated blood

C (Table 5). To control this study still further, 7 subjects showing evidence of porphyrinuria were given niacin-free synthetic vitamin B complex tablets composed of the following: thiamin hydrochloride 1.5 mg.; riboflavin 2.2 mg.; pyridoxin 1.5 mg.; and calcium pantothenate 10 mg. The amount of thiamin hydrochloride and riboflavin in each tablet corresponded to the daily requirement of these vitamins according to the National Research Council Committee on Foods and Nutrition. The dosage of the pyridoxin and calcium pantothenate in each tablet was in accordance with Williams' prescription of the daily requirement of these components of the vitamin B complex. Each of the 7 subjects received 2 of the tablets daily, or a double dose of the daily requirement, for 7 days. In none of the individuals was the test negative for the excretion of porphyrins for 2 successive days (Table 6). An attempt was also made to induce porphyrinuria by placing some of the subjects upon a niacin-free diet. But this phase of the experiment had to be discontinued when the individuals refused to remain on the restricted diet.

Comment. In a group of so-called normal aged individuals who showed evidence of porphyrinuria, the administration of niacin resulted in the disappearance of the ether-soluble red pigments from the urine. The explanation of this phenomenon is still debatable. Spies and his coworkers,¹⁵ as well as Turner,¹⁶ stated that when either niacin or its amide was administered to an individual showing porphyrinuria, the latter condition disappeared. This occurred in disorders such as pellagra, diabetes, and Roentgen ray disease. Dobriner and Rhoads,³ on the other hand, claimed that there was no close relationship between a lack of niacin and an increased excretion of ether-soluble red pigments. Kark and Meikeljohn⁶ stated that while alcoholic pellagrins occasionally exhibited an increased excretion of ether-soluble red pigments, this porphyrinuria was by no means a constant finding and bore no relationship to pellagrous dermatitis or to prolonged exposure to sunlight. Gross and his coworkers⁵ demonstrated that niacin cleared up the porphyrinuria which was present in 7 painters suffering from lead poisoning. Dobriner, Strain and Localio⁴ suggested that porphyrinuria may be a consequence of some liver dysfunction since they did not find an increased excretion of urinary porphyrins to be an essential feature of pellagra. Brugsch² stated that porphyrinuria may be caused by liver dysfunction, as a result of a deficiency of niacin, which would be just sufficient to prevent the normal functioning of the liver, but not enough to produce clinical manifestations. In our subjects, the disappearance of the porphyrinuria after the administration of niacin might possibly be explained on the basis of a subclinical deficiency of this vitamin. In a previous paper we showed that normal, aged individuals were lacking in ascorbic acid.¹⁰ Clinical experience has shown that a deficiency in one vitamin often indicated deficiency in the other vitamins. But, on the other hand, the normal excretion of niacin by our subjects did not seem to bear out the deficiency theory. The contention

that niacin corrects the liver function and thereby exerts a beneficial effect on the porphyrinuria seems the most likely explanation. This is suggested by the fact that in determining the cholesterol partition in the normal aged, we found the percentage of free cholesterol in whole blood to be higher and the percentage of cholesterol esters to be lower than those reported in normal individuals below 60 years of age.¹¹ We also observed, in making a comparative study of various liver function tests in a group of 50 normal aged individuals, that a positive test for hepatic impairment was obtained in 86% of the subjects.¹² Hepatic impairment is probably a normal condition in the aged, and porphyrinuria may be an indication of this. The addition of niacin probably improves the hepatic function. In this connection Sebrell¹⁴ suggested that niacin, instead of being directly associated with the metabolism of hemoglobin (which is the source of the porphyrins), acts either as a provitamin, or may be conjugated in the body with other substances into a more complex material. He further stated that the latter is the more tenable theory, since Warburg's enzymes, diphosphonucleotide and triphosphonucleotide, each contain a molecule of niacin.

Summary. 1. The administration of niacin to a group of normal, aged individuals resulted in the disappearance of porphyrinuria.

2. The niacin was stored by the body for an average of 4.5 days, as evidenced by a return of the porphyrinuria.

3. In a control series, which did not receive niacin, no decrease in the porphyrinuria was observed.

4. Niacin excretion in the aged individuals in this study was found to run approximately at the same levels in all subjects.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT

VI. FAILURE OF RIBOFLAVIN THERAPY IN PATIENTS WITH THE
ACCEPTED PICTURE OF RIBOFLAVIN DEFICIENCY

BY THOMAS E. MACHELLA, M.D.

INSTRUCTOR IN MEDICINE AND PHYSIOLOGY, UNIVERSITY OF PENNSYLVANIA MEDICAL
SCHOOL; RESEARCH FELLOW, PHILADELPHIA GENERAL HOSPITAL

AND

P. ROBB McDONALD, M.D.

INSTRUCTOR IN OPHTHALMOLOGY, UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL
PHILADELPHIA, PA.(From the Gastro-Intestinal Section [Kinsey-Thomas Foundation] of the Medical
Clinic and the Ophthalmology Clinic, University of Pennsylvania Hospital, and
the Thompson Vitamin Clinic of the Philadelphia General Hospital)

DURING the past few years certain subjective and objective clinical disturbances have been ascribed to a deficiency of riboflavin and have been reported to disappear when that vitamin is administered. As a result a description of a syndrome of "ariboflavinosis" has found its way into at least one modern textbook of medicine,² and the affection has been accorded a high incidence in some parts of the country. The present paper reviews the literature on the subject and summarizes personal experience in the treatment with riboflavin of some of the lesions attributed to its deficiency. Since, however, much of the data in the literature has been found to be conflicting and many of the lesions under our observation have failed to respond satisfactorily to the administration of riboflavin it is believed by us that the existence of a true syndrome of ariboflavinosis in the human is not yet established.

Analysis of Literature. The clinical phenomena that have been attributed to a deficiency of riboflavin are: (1) a cheilosis; (2) a seborrheic type of dermatitis, found in the nasolabial folds, on the alae nasi, in the vestibule of the nose and on the ears; (3) a vascularizing keratitis, manifested by dimness of vision, photophobia, lacrimation and burning and, on slit-lamp examination, by corneal vasculization; (4) a specific form of glossitis, characterized by a purple-red or magenta color of the tongue and by enlargement or flattening of its filiform papillae. Pemphigus vulgaris, though not attributed to a deficiency of riboflavin, has been reported to respond favorably to its administration.

1. *Cheilosis.* A characteristic lip lesion was observed by Sebrell and Butler¹⁷ to develop in 10 of 18 patients on a diet deficient in riboflavin and nicotinic acid and to heal when synthetic riboflavin was administered. It did not respond to nicotinic acid alone. Subsequently, in certain instances of suspected deficiency, the cheilotic lesion was observed to heal when either riboflavin^{7,13,18,23} or the B complex^{7,21} or both together¹² were administered. In most of the

above instances the lesion was believed to be due to riboflavin deficiency. Some of the data, however, permit skepticism as to whether or not riboflavin had anything to do with the disappearance of the lesion. For instance, the lesion in Sydenstricker's Case 2 healed while nicotinic acid alone was being administered, and that of his Case 5 first healed before any riboflavin was administered. From the observation of others it has become evident that the administration of fractions of the B complex other than riboflavin may be accompanied by healing of the lip lesion. Smith¹⁹ and Machella⁹ observed healing when pyridoxine alone was administered. Some cases have responded favorably to nicotinic acid alone and some have failed to respond to either riboflavin or pyridoxine or nicotinic acid, and have healed only when the entire B complex was administered. Furthermore, certain of the lesions, especially the hemorrhagic ones, have healed only when a scorbutic state was corrected (Machella⁹).

2. *Dermatitis*. Sebrell and Butler¹⁷ first reported the development in their subjects on a diet deficient in riboflavin and nicotinic acid of a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the naso-labial folds, on the alæ nasi, in the vestibule of the nose and on the ears. These authors, however, did not state very clearly whether or not this lesion disappeared when riboflavin was administered and published none of the details concerning healing. A similar affection was said by Oden¹³ to disappear when riboflavin alone was administered. Jolliffe⁷ claimed that a more advanced stage of this skin lesion, occurring at similar sites, consisted of filiform excrescences. This type, according to Smith,²⁰ does not respond to riboflavin, disappears slowly when nicotinic acid is administered and heals most promptly when the patient receives autoclaved yeast. Another type of facial skin lesion somewhat different from that originally described by Sebrell and Butler and ascribed to riboflavin deficiency was called by Spies²² "shark skin" and consists of a roughening of the skin around the mouth and across the tip of the nose. The pores of the affected areas are filled with sebaceous material.

3. *Keratitis*. An ophthalmic affection ascribed to riboflavin deficiency consists of a superficial vascularizing keratitis.^{8,24} It is manifested subjectively by dimness of vision, photophobia, lacrimation and burning. Slit-lamp examination reveals circumcorneal injection and superficial corneal opacities. The subjective and objective manifestations are alleged to disappear while riboflavin is being administered and to recur when this vitamin is no longer supplied. Prompt healing of this type of keratitis, associated with the rosacea syndrome, was observed in 32 out of 36 cases reported by Johnson and Eckardt⁵ when the patients received riboflavin. Rones and McKay¹⁴ found that also a type of non-vascular keratitis may respond to riboflavin. On the other hand, Spies²² claims that

ocular symptoms somewhat similar to those described by Sydenstricker may disappear when vitamin A is administered. It is also interesting to note that, although a vascularizing keratitis was observed in experimental animals on a riboflavin deficient diet by Bessey and Wolbach¹ and by others, no such lesion was observed to develop in Sebrell and Butler's human subjects on a diet deficient in this vitamin.

4. *Glossitis*. A specific form of glossitis also has been ascribed to riboflavin deficiency: the tongue is purple-red or magenta in color¹⁶ and the filiform papillae are flattened out or mushroom shaped.^{6,8,24} The evidence for such a lesion being due to riboflavin deficiency is not clear. It was not observed to develop in Sebrell and Butler's experimental subjects. Rosenblum and Jolliffe¹⁵ recently found the magenta color of the tongue uninfluenced by the administration of riboflavin in some patients, while in one instance the tongue was restored to normal by pyridoxine and in others by the administration of the entire B complex. Weisberger²⁶ ascribed an altogether different appearance of the tongue to riboflavin deficiency. In his cases, the tongue first became coated, this being followed by a patchy desquamation, usually oval in shape, the center of which was atrophic and the periphery raised. Although large oral doses of riboflavin were ineffective, restoration to normal was obtained by him when small doses were given intravenously.

5. *Pemphigus Vulgaris*. Topping and Knoefel²⁵ reported the successful use of riboflavin in a patient with pemphigus vulgaris, but this was not confirmed by the experience of Wolf and Lewis.²⁷

Description of Cases and Procedure. The 20 subjects for our study were patients in the wards and out-patient departments of the University of Pennsylvania and of the Philadelphia General Hospitals. Three of them had more than one lesion that has been ascribed to riboflavin deficiency. Patient D. C. had the cheilosis, the magenta-colored tongue with enlarged papillae, corneal opacities and conjunctival injection. She had no corneal vascularization, but a marked arcus senilis was present which, according to Sydenstricker, forms a barrier to vascularization at the limbus. Patients A. L. and R. G. had both the cheilosis and the magenta-colored tongue with flattened papillae.

Nine of the 20 subjects had the eye lesions, with both subjective and objective manifestations, which Sydenstricker and others have claimed should disappear when riboflavin is administered. Five of the total group had cheilosis. Six had glossitis, and 4 had pemphigus vulgaris.

A synthetic riboflavin* was administered orally. The dose during the first week or two was 2 mg. in tablet form 3 times daily. If no response occurred at the end of such a time, the amount of riboflavin was increased. The achlorhydric patients received in addition

* Generously supplied by Merek and Company, Inc., Rahway, N.J.

TABLE 1.—CASES OF CHEILOSIIS THAT FAILED TO RESPOND TO RIBOFLAVIN

Case	Age Sex Race	False teeth	Duration of lesion (mos.)	Other manifestations of deficiency	Riboflavin		Also failed to respond to (mg. in days)	Finally responded to: Brewer's yeast, 3.5 gm. t.i.d. in 21 days
					Daily dose (mg.)	No. of days		
D. C.	75 F W	+	6	Anorexia, glossitis, low blood as- corbic acid level, keratitis	6	7	B ₆ , 2100 in 14; N.A., 2100 in 7; C., 2625 in 14	
					6	14*		
					12	14*		
					15	7*		
F. M.	56 F W	0	12	Anorexia, glossitis, positive tour- niquet test, bleeding gums	12	14*	B ₆ , 700 in 14; C., 211 in 14	Brewer's yeast, 3.5 gm. t.i.d. in 14 days
A. L.	62 F W	+	8	Anorexia, glossitis, calf muscle tenderness	16	7	B ₆ , 4200 in 35	Brewer's yeast, 3.5 gm. t.i.d. in 10 days
					12	7*		
M. P.	55 F W	+	24	Glossitis	7.5	66	Brewer's yeast, 3.5 gm. t.i.d. in 7 days
R. G.	53 F W	0	4 (?)	Anorexia, glossitis, calf muscle tenderness	6	5*	Brewer's yeast, 3.5 gm. t.i.d. in 7 days
					12	5*		

* Period during which patient received 1 cc. of dilute hydrochloric acid with each meal.

at least 1 cc. of dilute hydrochloric acid with each meal. If no favorable response occurred after the combined therapy, another vitamin was prescribed and the riboflavin discontinued. No other vitamin supplements were permitted while the effect of one vitamin was being observed. No change in the dietary habits of the out-patients was allowed while under the vitamin treatment. In those patients admitted to the wards, however, access to a house diet was allowed. Such a diet satisfied the daily vitamin A and riboflavin requirements as recommended by the Committee on Foods and Nutrition of the National Research Council,³ providing all the food proffered over a 24-hour period was ingested.¹⁰ All of the patients with an eye lesion received, besides the vitamins, such local therapy as atropine and heat. Colored photographs of all lesions observed, as well as slit-lamp examinations of the corneal lesions, were made periodically. Greater detail as to the lesion characteristics are presented in the accompanying tables.

Results. 1. *Cheilosis.* One⁹ of us has previously reported negative results in the treatment of 8 cases of cheilosis with riboflavin. Since then 5 additional cases have been so treated and with equally negative results. One of the patients (D. C.) also failed to respond favorably to subsequent separate courses of pyridoxine and of nicotinic acid and to the correction of a scorbutic state, but the lesion did heal when brewer's yeast was administered. This patient had, in addition to the cheilosis, a purple-red tongue with enlarged papillæ and an ophthalmic lesion which also were refractory to riboflavin. In a second patient (F. M.) the lip lesion remained unhealed during subsequent separate courses of pyridoxine and of ascorbic acid. She also finally responded favorably to brewer's yeast. The lesion of a third subject (A. L.), who also had a purple-red tongue with enlarged filiform papillæ, remained unhealed despite a subsequent course of pyridoxine, and healed only when the entire B complex was supplied. The lesions in patients M. P. and R. G. healed promptly when brewer's yeast was substituted for the riboflavin (Table 1).

TABLE 2.—CASES OF PEMPHIGUS VULGARIS TREATED WITH RIBOFLAVIN

Case	Age Sex Race	Type of pemphigus	Duration of lesions in mouth	Riboflavin		Response
				Daily dose (mg.)	No. of days	
A. R.	74 M	Acute	2	6	4	0
	W					
F. K.	50 F	Acute	3	30	14	0
	W					
J. B.	79 M	Acute	4½	60	7	0
	W					
M. R.	45 F	Chronic	11	6	7	0
				18	14	
	C			54	7	

2. *Dermatitis*. We have had no significant experience in the treatment of the lesions of the face that have been ascribed to a deficiency of riboflavin. The administration of riboflavin to 3 acute and to 1 chronic case of pemphigus, however, brought about no improvement in the character or decrease in the number of the lesions. The 3 patients with the acute form of the disease died while under observation (Table 2).

3. *Keratitis*. The results of treatment with riboflavin in the 9 patients with corneal lesions were disappointing (Table 3). Only one of them (T. B.) experienced permanent subjective improvement, and even in him no objective change was observed. Five patients (H. T., N. T., M. C., M. H. and W. M.) at first showed temporary subjective and objective improvement but relapsed while the riboflavin therapy was continued. The cutaneous rosacea of the 5 patients with rosacea keratitis was uninfluenced by the vitamin during its period of administration.

4. *Glossitis*. Six patients with a purple-red or magenta-colored tongue and with flattened or mushroom shaped filiform papillae were treated with riboflavin. One of these (D. C.) had in addition a cheilosis and a lesion of the eye. In none of them was the appearance of the tongue significantly altered by the administration of the vitamin; in 4 (P. B., R. G., B. S., D. C.) a return to normal occurred after brewer's yeast, and in 1 (A. L.) after pyridoxine was administered. In the 6th (M. A.) an opportunity to observe the results of vitamin therapy other than riboflavin was not afforded (Table 4).

Comment. In view of the successful results from the administration of riboflavin in various clinical conditions reported by others we were disappointed to observe no significantly favorable response in our cases. The potency of the synthetic riboflavin that we used was indicated by the fact that it was effective in the prevention of alopecia in rats maintained on a B complex deficient diet. Furthermore, it was the same preparation stated to be beneficial by other workers. That patients were absorbing or utilizing the material satisfactorily was answered by finding in all instances the characteristic fluorescence when the urine was exposed to ultraviolet light. Furthermore, because Johnson and Eckardt⁵ noted that their cases of rosacea keratitis which failed to respond to riboflavin had achlorhydria, we administered dilute hydrochloric acid in all of our achlorhydric patients. The mechanism which accounts for the failure of the achlorhydric patient to absorb or utilize the vitamin is not clear.

As to the adequacy of the dosage employed, the daily amounts regarded as effective by some of the other workers were as follows: in the treatment of cheilosis, 1 to 2 mg.,¹⁷ 3 to 5 mg.;^{21,22} and in the treatment of ocular lesions, 3 to 5 mg.²⁴ None of our patients, however, received less than 6 mg. daily, in divided doses, and if no response occurred within a week or two the dosage frequently was increased.

TABLE 3.—CASES WITH OCULAR LESIONS TREATED WITH RIBOFLAVIN

Case	Age Sex Race	Ophthalmologic diagnosis	Subjective				Objective			Riboflavin		Improvement Subjective	Objective
			Burning photophobia lacrimation	Conjunctival injection	Corneal vascu- larization	Corneal opacities	Absolute achlorhydria	Daily dose (mg.)	No. of days				
L. C.	24 F C	Vascularizing keratitis	+	+	+	+	+	+	6	14	0	0	
D. C.	75 F W	Chronic conjunctivitis	+	+	0	+	+	+	6 12 14* 15	7 14* 14* 7*	0	0	
T. B.	52 M W	Vascularizing keratitis	+	+	+	0	+	0	2 6	7 14	+	0	
H. T.	65 F W	Chronic conjunc- tivitis, corneal ulcer O.D.	+	+	0	+	+	?	15	14*	0	0	
N. T.	18 M W	Rosacea, keratitis	+	+	+	+	+	+	6 6 12 12† 2 4 6	7 23* 30* 14* 7 7* 21*	0	0	
W. M.	37 F W	Rosacea, keratitis	+	+	+	+	+	+	2 6	21 14*	0	0	
M. C.	33 F W	Rosacea, keratitis	+	+	+	+	+	+	6	180*	0	0	
E. F.	63 F W	Rosacea, keratitis	+	+	+	+	+	+	6† 6 14	7 14 7	0	0	
M. H.	45 F W	Rosacea, keratitis	+	+	+	+	+	+					

* Period during which patient received 100 mg. of riboflavin daily.

* Period during which patient received 1 cc. of dilute hydrochloric acid with each meal.
 † Riboflavin administered intramuscularly.

TABLE 4.—CASES OF GLOSSITIS THAT FAILED TO RESPOND TO RIBOFLAVIN

Case	Age Sex Race	Appearance of tongue		Other manifestations of deficiency	Riboflavin		Responded to	Primary diagnosis
		Color	Filiform papillae		Daily dose (mg.)	No. of days		
D. C.	75	Purple-red	Enlarged	Corneal opacities, conjunctival injection, anorexia, calf mus- cle tenderness, cheilosis, posi- tive tourniquet test	6	7	Brewer's yeast, 3.5 gm. t.i.d. in 7 days	Avitaminosis (B complex and vitamin C), achlorhydria Achlorhydria
	F				6	14*		
	W				12	14*		
P. B.	50	Purple-red	Enlarged	Anorexia, calf muscle tender- ness	15	7*	Brewer's yeast, 3.5 gm. t.i.d. in 10 days	Chronic glomeru- lonephritis
	M				15	14*		
M. A.	28	Purple-red	Enlarged	Anorexia, cheilosis, calf muscle tenderness	13	7	Pyridoxine, 50 mg. t.i.d. in 7 days	Diabetes mellitus, angina pectoris
	F				16	7*		
A. L.	62	Purple-red	Flattened out	Anorexia, cheilosis, calf muscle tenderness	12	7*	Brewer's yeast, 3.5 gm. t.i.d. in 7 days	Hypertensive car- diovascular disease
	F				6	5*		
R. G.	53	Purple-red	Flattened out	Anorexia, calf muscle tender- ness	12	4*	Brewer's yeast, 3.5 gm. t.i.d. in 8 days	Laennec's cirrho- sis
	F				12	10*		
B. S.	51	Purple-red	Enlarged		12	10*		
	M							
	W							

* Period during which patient received 1 cc. of dilute hydrochloric acid with each meal.

A critical examination of the reports on some of the cases in which a riboflavin cure has been claimed reveals that in several instances the conclusions as to specific etiology are scarcely justifiable. For example, evidence is gradually accumulating that the cheilosis is non-specific, since in some instances it appears to respond to riboflavin, in others to pyridoxine, nicotinic or ascorbic acid, and at times only to the entire B complex. Furthermore, some cases of cheilosis resist vitamin therapy of any type, and indeed the lesion has been reported as being due to sensitivity to the flavoring matter of chewing gum¹¹ as well as to the eosin dye in lipstick.⁴

The rôle of improperly fitting artificial dentures in the production of cheilosis requires evaluation. Fourteen out of our 23 patients with this lesion had both upper and lower plates. At first we were inclined to look upon such individuals as especially predisposed to a vitamin deficiency because of their inability to masticate such foods as meat. It is possible that a closer apposition of the upper and lower limbs of the lips at the angles of the mouth as a result of an absence of teeth or even after the prolonged wearing of artificial dentures may predispose to the development of such a lesion. The discrepancies in the literature with regard to the dermatitis and the glossitis ascribed to riboflavin deficiency have already been referred to. Our series serves to emphasize the fact that certain cases, with the subjective and objective manifestations ascribed to riboflavin deficiency, do not improve when riboflavin is administered.

Conclusion. The conflicting data in the literature and our personal experience with 20 cases of so-called ariboflavinosis with lesions of the lips, cornea and tongue usually ascribed to a deficiency of riboflavin make us doubt the validity of this syndrome.

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RELATIVE ABSORPTION AND CONJUGATION OF 9 COMPOUNDS BY HUMANS DURING A 3-HOUR PERIOD*

(FREE AND CONJUGATED BLOOD LEVEL DETERMINATIONS DURING
A 3-HOUR PERIOD FOLLOWING PERORAL ADMINISTRATION OF
THE ACID SALTS ALONE, THE ACID SALTS WITH SODIUM BI-
CARBONATE, AND THE SODIUM SALTS OF SULFAPYRIDINE,
SULFATHIAZOLE, AND SULFADIAZINE)

BY ELMER H. LOUGHLIN, M.D.

RICHARD H. BENNETT, M.D.

MARY E. FLANAGAN, B.S.

AND

SAMUEL H. SPITZ, M.D.

BROOKLYN, N. Y.

(From the Department of Internal Medicine, Long Island College of Medicine)

SINCE the introduction of the sulfonamide compounds, many studies on their absorption, excretion, and distribution in the tissues have been reported. However, with a few exceptions, in the studies on absorption as determined by levels which these substances reached in the blood, observations have rarely begun before 1 hour after the administration by mouth.¹ Sadusk and his collaborators² have made observations as early as $\frac{1}{2}$ hour. Blood level determinations in dogs have been made as early as 15 minutes after oral administration, but these were confined to the free drug, since it was stated that conjugation of the sulfonamide compounds occurred only slightly in dogs.³ No determinations of both free and

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conjugated sulfonamides in the blood of human subjects have been made before $\frac{1}{2}$ hour. It was felt, therefore, that it would be informative to determine the time of appearance of the sulfonamides in the blood as free and possibly as conjugated forms after peroral administration in humans.

This article is devoted to the study of free and conjugated sulfonamide levels obtained in the blood at 5-minute intervals during the first $\frac{1}{2}$ hour and at 10 and 15-minute intervals during the remainder of the 3-hour period after the administration by mouth to human subjects of the acid and sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine.

Methods and Materials. The subjects were ward patients who were ill with various conditions or who had recently convalesced from acute illnesses. Ten subjects were used for each salt in the human series. They had not received any sulfonamide compound within 7 to 10 days before starting the experiment. They were fasted from supper of the evening previously; they did not receive any breakfast, and no fluids other than that which accompanied the administration of the drug were given.

The acid salts were suspended in 4 ounces of tap water, making certain that the entire amount was given. These were given alone in single doses of 4 gm., and in single doses of 4 gm. accompanied by an equivalent quantity of sodium bicarbonate. The sodium salts were dissolved in 4 oz. of tap water and were given in single doses of 4 gm.

Blood was taken for determination of free and total sulfonamide at intervals of 5 minutes during the first $\frac{1}{2}$ hour after administration, at 10-minute intervals during the second $\frac{1}{2}$ hour, and at 15-minute intervals during the second and third hour.

Determinations of the free and total sulfonamide in the blood were carried out according to the procedure of *Summerson* and *Litchfield*, employing in most instances a Klett-Summerson photoelectric colorimeter with a No. 54 filter.

Observations. Blood concentrations in human subjects during a 3-hour period following peroral administration of single 4-gm. doses of the sulfonamide compounds.

Sulfapyridine (Chart 1). Sulfapyridine was found in small amounts in the blood in 4 of 10 determinations, 5 minutes after the acid salt alone had been given, in 2 of 9 determinations after the acid salt with sodium bicarbonate, and in 7 of 9 determinations after the sodium salt had been given.

At 5 minutes in 2 of the 4 determinations in those subjects receiving the acid salt alone, both free and conjugated forms were found in the blood. The conjugated form alone was found in 1 subject given the acid salt with sodium bicarbonate and in 2 of those given the sodium salt.

Within 20 minutes after administration, all subjects given the acid salt had determinable sulfonamide in the blood. In those given the acid salt with sodium bicarbonate, all had the sulfonamide in the blood within 10 minutes, and in those receiving the sodium salt, the sulfonamide was present in the blood within 10 minutes.

Sulfathiazole (Charts 2, 3, 4). Determinable amounts of sulfathiazole were present in the blood in 2 of 10 determinations 5 minutes after the acid salt alone had been given, in 4 of 10 determinations

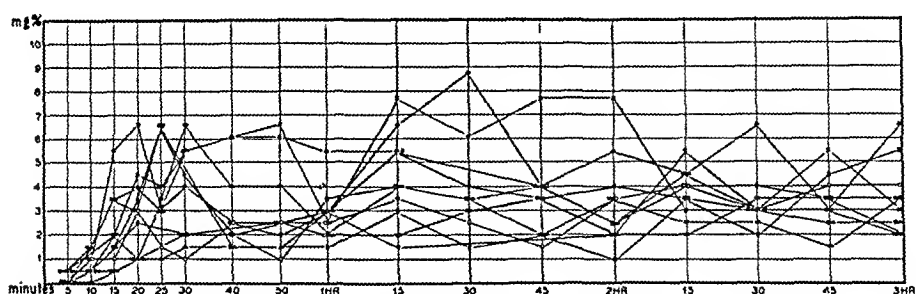


CHART 1.—Free blood levels of sulfapyridine after a single 4 gm. peroral dose of the sodium salt of sulfapyridine.

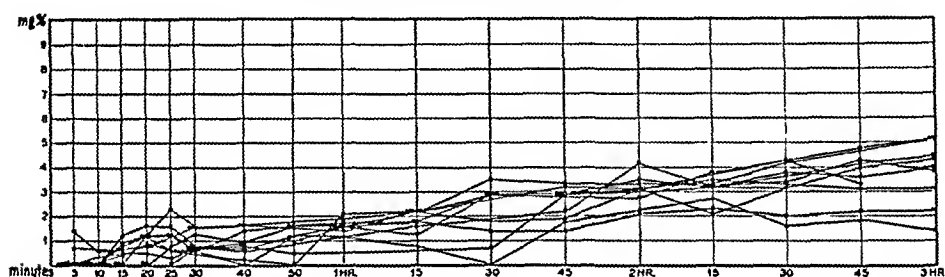


CHART 2.—Free blood levels of sulfathiazole after a single 4 gm. peroral dose of the acid salt of sulfathiazole.

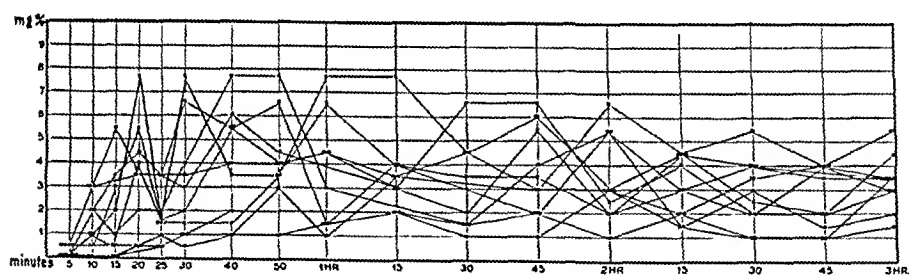


FIG. 3.—Free blood levels of sulfathiazole after a single 4 gm. peroral dose of the sodium salt of sulfathiazole.

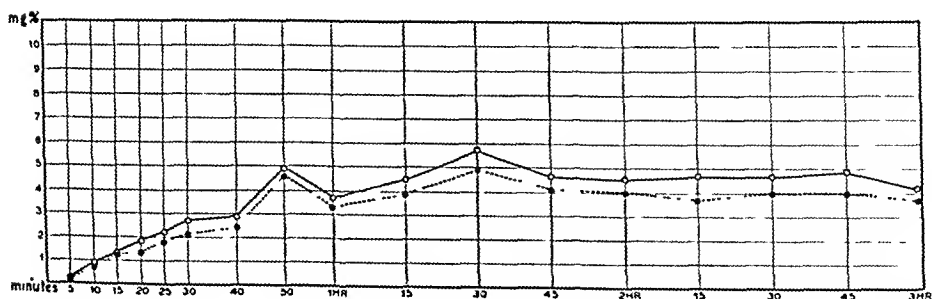


CHART 4.—Average free and total blood levels of sulfathiazole after a single 4 gm. peroral dose of the acid salt of sulfathiazole administered with 4 gm. of sodium bicarbonate. Dotted line = free; solid line = total (free + conjugated).

after the acid salt with sodium bicarbonate had been given, and in 6 of 10 determinations after the sodium salt had been given.

In 1 of the 2 determinations in 5 minutes of those subjects receiving the acid salt alone, both free and conjugated forms were found in the blood. The conjugated form alone was found in the blood in 1 subject receiving the acid salt with sodium bicarbonate and in 2 of those given the sodium salt.

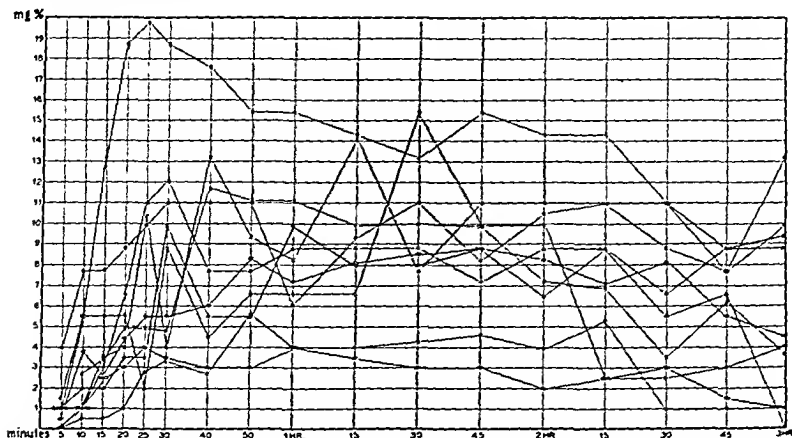


CHART 5.—Free blood levels of sulfadiazine after a single 4 gm. peroral dose of the sodium salt of sulfadiazine.

In all subjects given the acid salt alone there was determinable sulfonamide in the blood in 30 minutes and in all those receiving the sodium salt alone and the acid salt with sodium bicarbonate, all had sulfonamide in the blood within 15 minutes.* In 2 subjects determinable sulfathiazole was found at 2 minutes after administration. It then disappeared and returned at 4 minutes and 10 minutes respectively. In the latter subject, no blood specimens were obtained from the 5-minute interval to the 10-minute interval. In 2 other subjects, free sulfathiazole was found at 3 minutes after the initial dose.

Sulfadiazine (Charts 5, 6, 7, 8). Sulfadiazine in small amounts was present in the blood in 4 of 10 determinations made 5 minutes after the acid salt alone had been given, in all of the 10 determinations after administration of the acid salt with sodium bicarbonate, and in 7 of 9 determinations after the sodium salt had been given.

In those subjects receiving the acid salt alone, both the free and conjugated forms were found in the blood in 3 of the 4 determinations

* In several subjects at the start of this study, determinations were made of the free levels reached in the blood at $\frac{1}{2}$ -minute intervals for the first 5 minutes after administration of a single dose of 4 gm. of sodium sulfathiazole. In 1 subject, a determinable amount of sulfathiazole appeared in the blood within 1 minute after administration. Blood taken at minute intervals for the next 4 minutes revealed no free sulfathiazole.

made. In those subjects receiving the acid salt with sodium bicarbonate, the conjugated form alone was found in 3 and both conjugated and free forms in 3. In those to whom sodium salt was administered, the free and conjugated forms occurred but once.

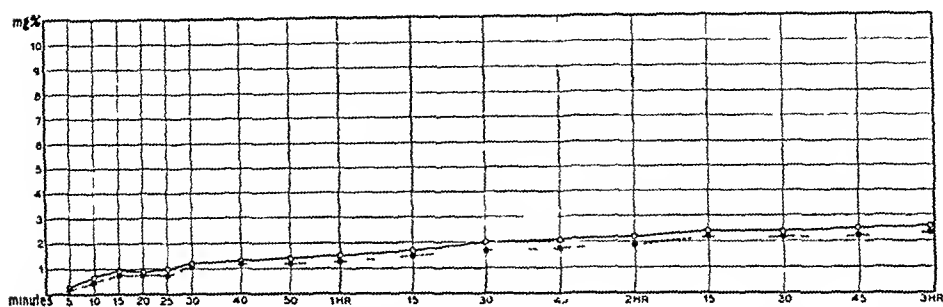


CHART 6.—Average free and total blood levels of sulfadiazine after a single 4 gm. peroral dose of the acid salt of sulfadiazine. Dotted line = free; solid line = total (free + conjugated).

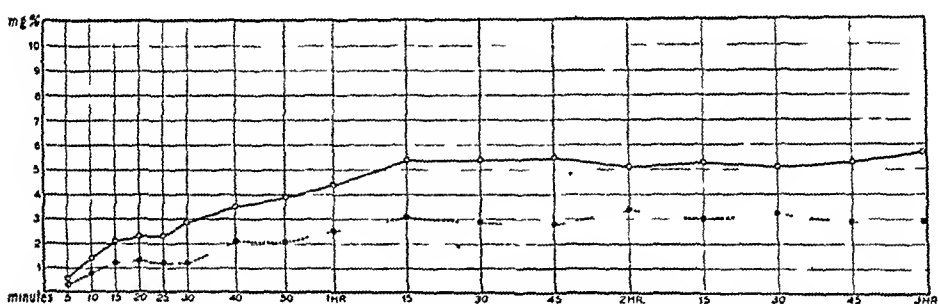


CHART 7.—Average free and total blood levels of sulfadiazine after a single 4 gm. peroral dose of the acid salt of sulfadiazine administered with 4 gm. of sodium bicarbonate. Dotted line = free; solid line = total (free + conjugated).

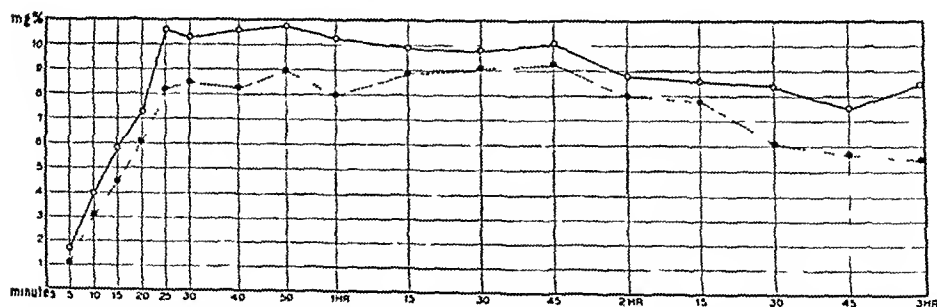


CHART 8.—Average free and total blood levels of sulfadiazine after a single 4 gm. peroral dose of the sodium salt of sulfadiazine. Dotted line = free; solid line = total (free + conjugated).

All subjects who were given the acid salt presented determinable sulfonamide in the blood within 15 minutes; whereas, in those receiving the acid salt with sodium bicarbonate, the sulfonamide was present in every instance within 5 minutes; and in those given the sodium salt it was present in all instances in 10 minutes.

TABLE 1.—RESULTS

(Blood Concentrations in Human Subjects During the 3-hour Period Following Peroral Administration of Single 4 Gm. Doses of the Sulfonamide Compounds)

Percentage of determinations showing drug in blood at 5 minutes as:

	Free alone	Free and conjugated	Conjugated	Total	Minutes*
Sulfapyridine	10	20	10	40	20
Sulfapyridine with sodium bicarbonate	0	11 1	11 1	22 2	10
Sodium sulfapyridine	50	0	20	70	10
Sulfathiazole	10	10	0	20	30
Sulfathiazole with sodium bicarbonate	20	..	10	40†	15
Sodium sulfathiazole	40	0	20	60	15
Sulfadiazine	10	30	0	40	15
Sulfadiazine with sodium bicarbonate	40	30	30	100	5
Sodium sulfadiazine	55 5	22 2	0	77 7	10

* Period after administration when all subjects had demonstrable drug in blood stream.

† Total level of drug was not obtained in one instance.

Fluctuations in the blood levels occurred in many of the subjects receiving the acid salts with sodium bicarbonate. This was particularly true in those receiving sulfadiazine and sulfathiazole. Wider fluctuations occurred with those receiving the sodium salts. This was especially marked in the case of sodium sulfadiazine. This would indicate that absorption of these three sulfonamides in an alkaline medium is anything but regular.

Summary and Conclusions. Experiments on man were made relating to the absorption of the acid and sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine, as evidenced by blood levels obtained at short intervals during a 3-hour period following administration.

The acid and sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine were rapidly absorbed from the gastro-intestinal tract, presumably from the stomach, as evidenced by their appearance in many instances as early as 5 minutes after peroral administration.

The absorption of the acid salts apparently is favored by simultaneous administration of an equal amount of sodium bicarbonate. The absorption of the sodium salt, as demonstrated by blood levels obtained, was more rapid and greater than the absorption of the acid salt alone or the acid salt with sodium bicarbonate.

The absorption of the acid salts with sodium bicarbonate and the sodium salts of these 3 sulfonamide compounds, as evidenced by fluctuating blood levels obtained at short intervals during the 3-hour period after administration, was irregular as compared to the absorption of the acid salts when given alone.

Conjugated forms were present in the blood as early as 5 minutes after peroral administration of the acid and sodium salts of these sulfonamide compounds; in some instances being the only form present.

Conjugation was more marked when the acid salts of sulfapyridine and sulfadiazine were administered with sodium bicarbonate, than when their respective acid salts were given alone.

There was less conjugation when the acid salt of sulfathiazole was given with sodium bicarbonate than when the acid salt alone was given.

The average degree of conjugation was greater when the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine were given than when their respective acid salts alone, or the acid salts with sodium bicarbonate were given.

We wish to express our appreciation to Dr. Tasker Howard for his careful criticism and suggestions throughout this study.

We wish to thank also Mr. Sidney M. Karlton for his coöperation in our study.

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THE OCCURRENCE OF ABNORMAL CAPILLARY FRAGILITY IN THE NEWBORN*

BY WILLIAM CURRY MOLONEY, M.D.

ASSISTANT PROFESSOR OF MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL,
BOSTON, MASS.

THE hemorrhagic disorders in the newborn have been the subject of renewed and intensive investigation since the development of improved methods for the study of prothrombin and the discovery of vitamin K. However as Quick⁷ has pointed out, for abnormal bleeding to occur there must not only be an interference with the coagulating mechanism of the blood but also a break in the vascular integrity. Recently MacFarlane⁵ has emphasized the vascular factor in hemostasis, stating that in hemorrhagic diatheses the bleeding tendency may be due to a combination of clotting and capillary defects. Since hemorrhagic tendencies and lowered prothrombin levels usually develop within the first week of neonatal life, this preliminary investigation was undertaken to determine if abnormal capillary fragility also occurred during this period.

* Read before the John Taylor Bottomly Society of the Carney Hospital, South Boston, Mass., April 7, 1942.

Methods and Material. The capillary resistance was studied in 55 newborn infants, consisting of a random mixed group of house and private cases. The method and instrument used were those of Dalldorf,⁴ the resistometer being attached to a negative pressure suction pump. Readings were made at -10, -20, and -30 cm. Hg. The back of the infant was exposed and gently sponged with aqueous Zephiran and allowed to remain moist. The glass suction cup was applied and, after one minute of suction, the petechiæ in the circle 1 cm. in diameter were counted. Care was taken to use a different area of the back, so that the tests were not superimposed at subsequent determinations. Tests were carried out within the first 24 hours and then every day until the fourth day. If negative, no further determinations were made; otherwise tests were repeated until the eighth day.

In the present study the following criteria were observed for grading capillary fragility:

- 0—no petechiæ.
- +—1 or 2 petechiæ at -20 and -30.
- ++—5 to 10 petechiæ at -20 or -30, or 1 to 2 petechiæ at -10.
- +++—over 10 petechiæ at -20 or over 2 petechiæ at -10.
- ++++—large numbers of petechiæ or free bleeding.

Comment. There have been valid objections to the use of this type of capillary fragility test; but in spite of imperfections, it offers the only procedure clinically available at present for this type of study. Comparatively little has been done on the study of capillary fragility in the newborn and there exists a wide divergence of opinion as to what normal findings are in childhood and in adults even when the same method is used. Thus Dalldorf⁴ states that, using the suction method, capillary resistance is normally between -30 and -40 cm. Hg. no matter what the age group.

In 1936 Abt *et al.*,¹ in a study on the relationship of vitamin C and capillary resistance, stated that "the skin of these newborn babies was ruddy, and petechiæ, or diffuse reddening of the skin, was not noted under 500 mm. of negative pressure." However, the tests in their report were made with a different type of apparatus (Cutler and Johnson), and there were apparently only 6 infants under 6 days of age tested; the youngest was 3 days old. Recently Brown² and Wasson, using Dalldorf's technique in children, indicate that one or two petechiæ occurring with the pressure below -15 cm. constitute a positive test.

The authors quote Abt and his co-workers, as does Dalldorf, to the effect that the newborn infant has an unusually high capillary resistance, a finding which is not consistent with the observations in this study.

Results. Despite reports in the literature indicating increased capillary resistance in the newborn, it was discovered that of this group of 55 infants only 22 showed no capillary fragility. Nine infants showed slightly positive tests; 12 had moderately severe, 8 severe, and 4 very severe reduction of capillary resistance (Chart 1).

Of even greater interest was the observation that the tendency to abnormal capillary fragility in these infants progressively de-

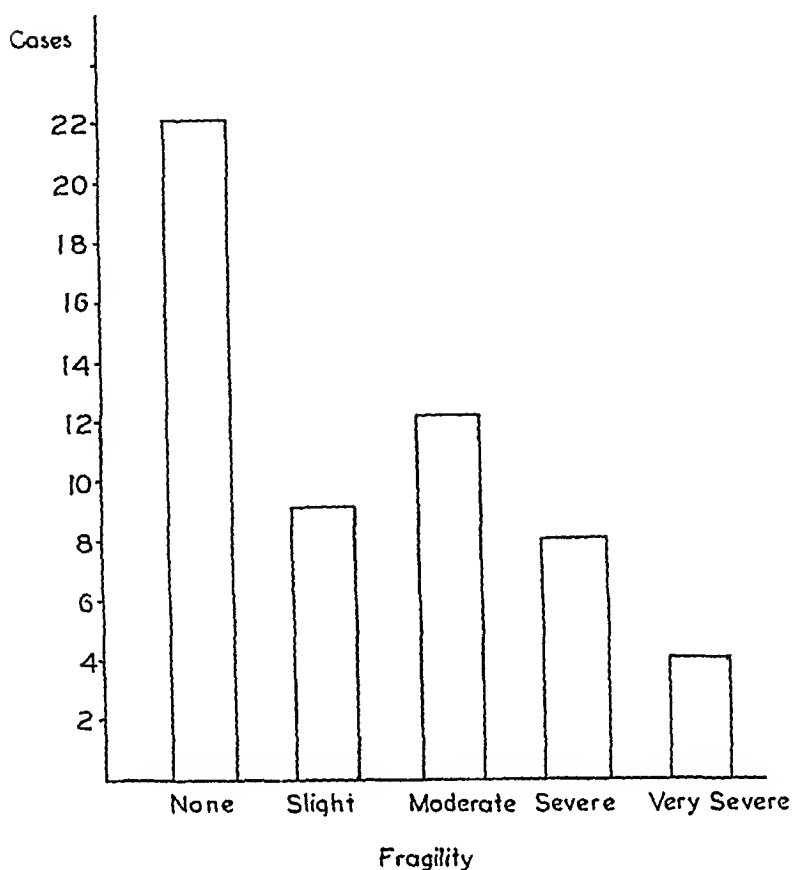


CHART 1.—Capillary fragility in the newborn.

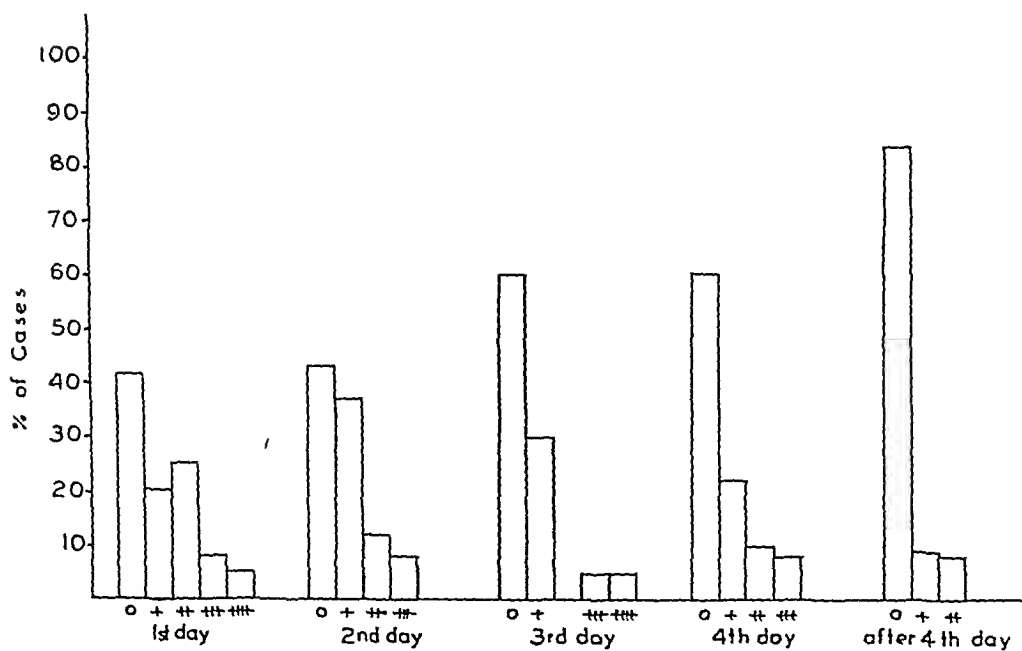


CHART 2.—Capillary fragility in the newborn—55 cases.

ereased postnatally, both qualitatively and quantitatively. Thus, there was a definite decline from a total of 56% positive tests of all degrees within the first 24 hours to a total of only 16% mildly positive tests after the fourth postnatal day. (See Chart 2.)

Discussion. Gross trauma is an obvious cause of vascular injury, but trauma may be a relative term; even normal functional pressure can produce capillary disruption if there is underlying weakness of the vascular endothelium. It is possible to tabulate many extrinsic and intrinsic factors which may damage the capillary wall: deficiency of vitamins C and P, the action of various capillary toxins, the type of skin, the platelet level, and prematurity of the infant should be considered. (See Table 1.)

TABLE 1.—POTENTIAL CAUSES OF DECREASED CAPILLARY RESISTANCE IN THE NEWBORN

- I. EXTRINSIC.
 - A. General.
 1. Seasonal changes.
 2. Temperature.
 3. Barometric pressure.
 - B. Maternal.
 1. Prenatal.
 - a. Deficiency of vitamins C and P.
 - b. Toxins, chemical, bacterial, nephrotoxins.
 2. Parturition.
 - a. Analgesia.
 - b. Anesthesia.
 - c. Duration of labor and type of delivery.
- II. INTRINSIC (infant).
 1. Prematurity.
 2. Type of skin.
 3. Hereditary or congenital capillary defects.
 4. Thrombocytopenia.
 5. Anoxemia.

However, the greatest interest centers about the process of parturition, and it is evident that the amount and kind of analgesia and anesthesia, the duration and character of labor, and the manner of delivery are factors of paramount importance in the potential production of abnormal fragility in the newborn. Information about the mother's age, parity, diet, and occurrence of toxemia, as well as data concerning the process of parturition, was obtained in this small series of cases. Although these data were not sufficient to permit an evaluation of the various factors, it is interesting to note that the duration of labor for the infants with severe and very severe capillary fragility averaged 14 hours, while the duration of labor for the moderate, slight, and negative groups was on the average approximately 5 hours. With few exceptions, the patients in this series had some analgesia and anesthesia, and it is obvious that more drugs and anesthesia were required in the group with prolonged and difficult labors.

It is possible that analgesic and anesthetic agents may have a direct toxic effect on the capillary endothelium, but it is far more

likely that the combined effects of labor, analgesia and anesthesia result in anoxia in the infant.

Clifford³ states that the effect of oxygen lack on the smaller cerebral vessels is to increase the fragility of the vessel wall and to produce actual leakage of red blood cells and even small hemorrhages. Nygaard⁶ points out that once failure of the capillary defense has initiated bleeding, the clotting mechanism, defective due to lack of prothrombin, may permit hemorrhage to continue and become clinically significant. Therefore, findings in this preliminary report of abnormally low capillary resistance in a number of infants during the period in which hypoprothrombinemia and hemorrhagic disorders occur most frequently may have a relationship to abnormal bleeding in the newborn.

Summary and Conclusions. 1. In a preliminary study of capillary resistance in the newborn, of 55 infants, 33 (60%) showed more or less abnormal capillary fragility.

2. This decreased capillary resistance disappeared as the infants became older.

3. Various factors influencing permeability of the capillary wall are outlined, and the possible relationship of abnormal capillary resistance to hemorrhagic disorders in the newborn is postulated.

Thanks are extended to Louis Phaneuf, M.D., Chief of the Obstetrical and Gynecological Service, and Paul Jakmauh, M.D., Chief of the Pediatric Service at the Carney Hospital, South Boston, Mass., for permission to carry out this study.

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BILATERAL PARTIAL BUNDLE BRANCH BLOCK*

By SIDNEY STRAUSS, M.D.

AND

RICHARD LANGENDORF, M.D.

CHICAGO, ILL.

(From the Cardiovascular Department, Michael Reese Hospital)

THERE are only a few cases on record of sinus rhythm with intraventricular block in which the type of the ventricular complex varied between the common and uncommon bundle branch block types (Winterberg;⁹ Barnes and Yater;¹ Stenström;⁷ Grassberger;² Katz,

* Aided by the A. D. Nast Fund for Cardiovascular Research.

Hamburger and Rubinfeld;³ Mortensen⁵). On this account it seemed worthwhile to report such a case seen recently, and to discuss the mechanism of the disturbed intraventricular conduction.

Case Report. This 58-year-old male was first seen by one of us (S. S.) in June, 1939, shortly after he had had a momentary fainting spell. On physical examination the heart was found to extend 3.5 cm. to the right and 12 cm. to the left of the midsternal line. There was a systolic murmur at the apex and over the aortic area. The aortic second sound was accentuated and ringing. At times there was a diastolic gallop rhythm. The pulse rate was 48 and during the examination changed to 108 on taking a deep breath. The blood pressure was 180/80 and changed to 174/104 when the pulse became rapid. The liver was palpable 2 fingers' breadth below the costal margin. There was a marked arcus senilis.

The probable presence of heart block raised the question of a recent coronary occlusion involving the branch supplying the bundle of His, and the patient was sent to the hospital at once. The physical findings in the hospital were the same as in the office. The electrocardiogram taken on entrance showed a rate of 107, a bundle branch block of the uncommon type, a P-R interval of 0.20 second. Records taken on subsequent days showed some minor changes—not enough, however, to warrant the diagnosis of a recent myocardial infarction. Nevertheless, he was treated as such and kept in bed in the hospital and at home for 5 weeks. His course was uneventful except for a mild recrudescence of his gout. The temperature was normal throughout. There were 13,550 leukocytes with 69% polymorphonuclear cells. The blood pressure varied from 190/130 on entrance to 155/100 on discharge. The Wassermann reaction was negative. The urine was normal.

On 7-17-39 the patient returned to his office. On 7-21-39 the findings on physical examination were about the same as before, except that there were no murmurs at the apex and no gallop rhythm. The physical findings remained unchanged until his death on 3-11-40. He never seemed to regain his strength although he was able to work up to 1-25-1940. He continued to have attacks of dizziness and fainting at long intervals, some while sitting in his office, some while walking in the street.

On 1-25-40 one of us (S. S.) was called to his home because of fainting spells which had started in his office and continued in his home. He was in bed, having had a series of convulsions, probably 20 or 30 in number which varied in duration from a few seconds to several minutes, giving rise to queer sounds and at times to vomiting and were associated with unconsciousness. He was given 1 cc. of 1:1000 adrenalin hydrochloride by hypodermic injection and in 15 to 20 minutes his pulse resumed its usual regular rhythm. After a few days in bed, he attempted, on advice, to sit up but the dizzy spells recurred on the least exertion. For the first time on 2-24-40 his slow pulse lasted long enough to get an electrocardiogram. This showed the A-V heart block. He was given ephedrine sulphate, gr. $\frac{3}{4}$ t.i.d., and for a week he was apparently much improved. Early in the morning of 3-11-40 he was heard groaning, the nurse found him unconscious and he died before medical aid could reach him.

Although the original diagnosis of a recent coronary occlusion was made, the subsequent course and the electrocardiographic findings did not corroborate this. The picture was more that of coronary sclerosis with gradual narrowing especially of the branches going to the bundle of His and its divisions. The usual picture of angina on effort was replaced by that of paroxysmal heart block on effort associated with Adams-Stokes syndrome. Death was due to the marked narrowing or final complete occlusion of these branches involving A-V conduction and not to the more usual infarction.

It is of interest that an older brother died of a similar disease involving the conduction system which led to heart block with Adams-Stokes syndrome for several years. A younger sister died with a typical myocardial infarction.

Autopsy Report. (Dr. Otto Saphir.) *Pathologic Diagnosis.* Marked coronary sclerosis with occlusion of the anterior descending branch, the ramus septi fibrosi, and narrowing of the ramus anterior ventriculi sinistri, and ramus marginis obtusi. Marked fibrosis of the myocardium. Slight narrowing of the ostium of the right coronary artery. Hypertrophy of the heart (slight—left and right ventricles). Chronic passive hyperemia of the liver, spleen and kidneys. Fibrosis of the spleen. Moderate emphysema of the lungs.

The heart weighs 400 gm. The epicardium and endocardium are smooth and glistening. The base of the mitral valve is somewhat thickened and presents several grayish-yellow plaques. The remainder of the valvular apparatus presents no abnormality. The myocardium of the left ventricle measures 1.3 cm. in thickness, that of the right ventricle 0.2 cm. at the pulmonic orifice, 0.1 to 0.2 cm. at the tricuspid, and 0.1 cm. at the left lateral margin. The epicardial fat in some areas is not sharply demarcated from the myocardium of the right ventricle. Both ventricular cavities are somewhat dilated. The lining of the coronary arteries is covered by numerous single and confluent grayish-yellow plaques. These have produced partial occlusion of the anterior descending branch 1 cm. from its origin and complete occlusion 4 cm. from its origin. Some narrowing is present at the point of bifurcation of the anterior descending and left circumflex branches. Further partial occlusions are noted throughout the left circumflex branch, ramus anterior ventriculi sinistri, and ramus marginis obtusi. The mouth of the right coronary artery is somewhat narrowed by sclerotic plaques. At the posterior crux the months of several arteries emanating from the right ventricle are completely occluded. Among these is probably the ramus septi fibrosi. The ascending portion of the aorta presents only a minimal number of plaques. These increase in number and maximally involve the lumbar portion of the aorta.

Microscopic Examination of the Heart. There is a diffuse slight to moderate increase in connective tissue throughout the myocardium. In addition there is a moderate invasion of fat tissue in some sections of the myocardium. The variously sized coronary arteries show moderate intimal thickening, vacuolization, degeneration and fibrosis. Septum: there is a marked increase in connective tissue throughout the myocardium. The arteries, small and large, show slight to moderate intimal thickening. Special muscular tissue: there is a diffuse slight to moderate increase in connective tissue throughout the A-V node, the A-V bundle, and the left arborization. In addition there are moderate to marked degenerative changes throughout the A-V bundle, the number of nuclei being less than is normally seen, and some fibers showing marked vacuolization (more than normally seen) with dissolution. Large fat vacuoles are present throughout the special muscular tissue. The fibers of the left and right arborization stain irregularly. Some of the nuclei are pyknotic and their cytoplasm very eosinophilic. Brown pigment granules are noted in many of the fibers. Two moderately sized arteries course through the A-V node, and one of these continues through the A-V bundle. Both of these are moderately narrowed by thickening of the intima.

Description of the Electrocardiograms. The records are shown in Figures 1 to 4. There is a sinus rhythm in all records, the sinus rate being 88, 86, 83 and 75 respectively. The P wave contour varies between records, the

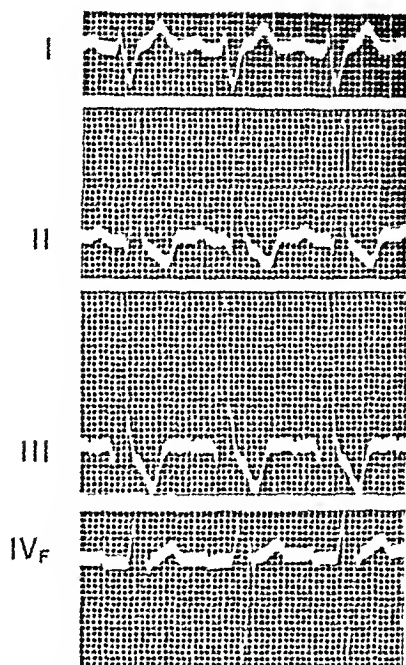


FIG. 1.—Sinus rhythm. P-R 0.21 second. QRS duration 0.16 second. Uncommon type of intraventricular block. 2-7-40.

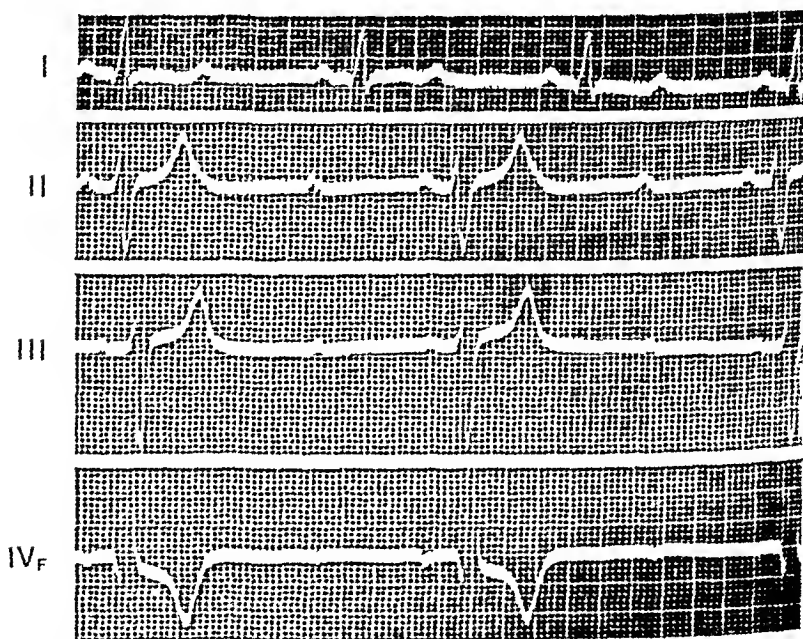


FIG. 2.—Sinus rhythm. Second degree A-V block varying from 2:1 in Lead I to 3:1 in the other leads. The direction of QRS has changed completely, the common type of intraventricular block is now present. 2-24-40.

most marked change being in the record taken on 2-26-40 (Fig. 3) where the P wave is of lower amplitude in I and II. The QRS measures 0.16 second in all records but its direction changes in the several records; the first (Fig. 1) and last (Fig. 4) record show the uncommon type of intraventricular block, the second (Fig. 2) and third (Fig. 3) record the common type of intraventricular block, but the second record differs from the third in its contour, QRS_i being lower in amplitude and W in shape. The first and last record (with uncommon intraventricular block) show a P-R interval at the upper limit of normal (0.21 second), the second and third record (with common intraventricular block) show a second degree A-V block varying from 2:1 to 3:1.

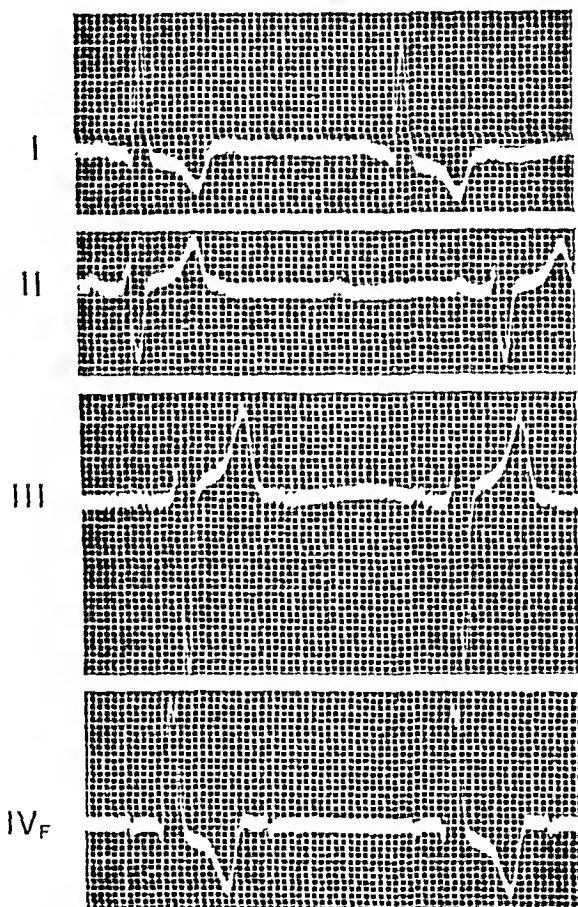


Fig. 3.—Sinus rhythm. Second degree A-V block varying from 2:1 in Lead I to 3:1 in the other leads. Common type of intraventricular block. 2-26-40.

Discussion. While intraventricular block is frequently regarded as involving only one bundle branch, actually it may involve both. When thorough histologic examination of the conduction system in cases of intraventricular block is made, both bundle branches are usually found to be involved (Mahaim;⁴ Yater, Cornell and Claytor;¹¹ Yater¹⁰). This would suggest that bilateral involvement might be more frequent than hitherto expected.

If complete* block is present in both bundle branches, complete A-V block results and the ventricles are controlled by an idio-ventricular pacemaker. This mechanism cannot be distinguished from other forms of complete A-V heart block due to a lesion of the conduction system above the bifurcation of the common bundle. The difficulty in distinguishing the degree of conduction disturbance

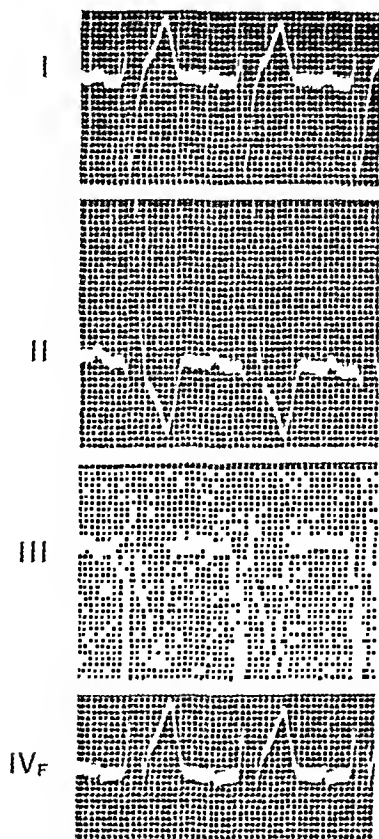


FIG. 4.—Sinus rhythm with 1:1 conduction. P-R 0.21 second. Uncommon type of intraventricular block. The record resembles the first record with 1:1 conduction (Fig. 1). 2-27-40. The streaks at the bottom of the record in Lead III at the time QRS is inscribed are artefacts.

present in involved bundle branches is shown by the experiments of Wilson and Herrmann,⁸ who found that partial block in one of the bundle branches of the dog's heart causing a delay in conduction of 0.04 second or more led to an electrocardiogram indistinguishable

* The terms "complete" and "partial" bundle branch block are used in the same sense as in A-V conduction, indicating absent response, or intermittent, or delayed response to the impulse respectively. They do not, and cannot, refer to the cross-section of the damaged bundle branch system. The misleading term "incomplete" bundle branch block is avoided.

from that seen after complete interruption of the same bundle branch. When complete interruption of one bundle branch was followed by temporary damage to the other branch,⁶ the configuration and duration of QRS remained unchanged from its appearance after complete interruption of the first bundle branch, and, in addition, A-V block appeared. Scherf and Shookhoff,⁶ by cutting one bundle branch and compressing the other between its upper and middle third, were able to produce various degrees of A-V block ranging from simple prolongation of the P-R interval to marked second degree or transient complete block. Thus, if complete block is present in one bundle branch system and partial block in the other, one might expect some evidence of impaired A-V conduction in addition to a prolonged QRS, since the P-R interval includes the time for the transmission of the impulse through the main bundle branches. A third possibility is partial block of both bundle branches. This will lead to a slight increase of the A-V conduction time or to a more marked degree characteristic of A-V block for the reason just mentioned. However, QRS will not necessarily be prolonged, providing the difference in delay in conduction *via* the two bundle branch systems is below the critical value. Only if this difference measures more than the critical value, 0.04 second in the dog, can the electrocardiogram be expected to be that of "complete" bundle branch block. The electrocardiographic type of bundle branch block will be determined by the refractory phase of the two bundle branch systems.

It is thus apparent that it may not be possible to determine whether a tracing with partial A-V block and a QRS of more than 0.12 second duration indicates (a) bilateral partial bundle branch block, (b) complete blockage of the impulse in one bundle branch system plus partial block in the other, or (c) unilateral branch involvement (partial or complete) plus additional properly located involvement of the common bundle or the A-V node.

The case here reported changed intermittently from the common to the uncommon type of intraventricular block, thus indicating the ability of either bundle branch system to transmit the impulse. Therefore, on the basis of the above discussion, the case would appear to fall into the category of bilateral partial bundle branch block.

The path taken by the impulse is determined by the duration of the relative and absolute refractory phase of the conducting tissue. In the two regions of block (A and B) assumed to exist in our case, the one (A) having a longer period of absolute refractoriness than the other (B) is assumed to have a much shorter period of relative refractoriness. An impulse arriving late enough to be conducted through to the ventricles is therefore conducted through region A with less delay than through region B with the shorter absolute refractory period. In our case it would appear that when every

auricular impulse got through to the ventricles (1:1 A-V conduction), the bundle branch system, presumably the right, which gives rise to the uncommon type of bundle branch block, was in a state of absolute refractoriness; and the impulse was conducted to the ventricles along the left bundle branch, which was only relatively refractory. However, when 2:1 or 3:1 A-V block was present as a result of additional block above the bifurcation of the common bundle, the impulse reached the bundle branch systems when they had both passed the state of absolute refractoriness but still were relatively refractory. Under such circumstances the bundle branch system, presumably the left, which gives rise to the common type of bundle branch block showed the greater refractoriness and hence the greater delay in conduction. The impulse, therefore, was conducted to the ventricles along the right bundle branch system and the common type of bundle branch block appeared in the electrocardiogram.

This explanation accounts for the findings observed in our case and can be readily applied to other cases in the literature. This analysis illustrates again how simple knowledge of the physiologic properties of the heart can be applied to account for seemingly complex arrhythmias. This interpretation indicates that cases like this can be taken as clinical evidence supporting the anatomic observation of the frequent involvement of both bundle branch systems.

Summary. A case is reported of sinus rhythm with intraventricular block showing variations of the ventricular complexes between the common and uncommon types. This change is associated with the occurrence of advanced partial A-V block. The alternations are explained by assuming partial block in the two main bundle branch systems with a shorter relative refractory phase of the bundle branch which has the longer absolute refractory phase.

We are indebted to Dr. L. N. Katz for suggestions and advice in preparing this report.

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THE PREDICTABILITY OF THE CHARACTER (INCREASED OR NORMAL) OF THE ERYTHROCYTE SEDIMENTATION RATE.

A SURVEY OF 1000 CASES

BY JOHN D. HELM, JR., M.D.

SENIOR RESIDENT IN MEDICINE, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA,
AND ASSISTANT INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

ALTHOUGH Galen knew nothing of the red blood cells or their sedimentation, he did recognize the "*crusta phlogistica*" as an evidence of disease. This same phenomenon of an increased buffy layer of clotted blood came to the fore again in the 18th century when it was called "the size." It was used as an indication for further bleeding, a fact which by itself helps to explain the excesses of the phlebotomists of that day as due to the vicious circle established between anemia and more rapid sedimentation. By 1772, Hewson had discovered the main facts about red cell sedimentation and its increase in disease. With all this knowledge, however, over a century had to pass before, in 1918, Fåhræus⁷ discovered the increased sedimentation rate in pregnancy and put the matter on a quantitative scientific basis. Since then, some 2500 articles have been written on the sedimentation rate and it would seem that the last word should have been said. However, it appears that after the long years of neglect the method is now perhaps being used too routinely. The present study has been carried out to learn whether the routine use of the test in general medical practice is justifiable, or whether its use should be limited to certain situations in which perhaps it should be repeated more often.

The literature of the past 25 years has stressed certain aspects of the use of this phenomenon in diagnosis, prognosis, and therapy. Cutler has stressed the point that the sedimentation rate is a non-specific phenomenon; indicates the presence of tissue destruction, and gives an index of the degree of systemic reaction to the disease present. He states that it has two chief values: 1, as a lead to the presence of tissue destruction, and 2, as a gauge of its severity.

The use of the sedimentation test has been advocated in many and various pathologic conditions. Cutler,³ in 1926, advocated its use to determine the activity of a tuberculous process; in 1932,⁴ reporting on observations on 5000 patients, he concluded that the sedimentation rate served its purpose as an indicator of the presence of organic disease. Schattenberg,¹⁸ also in 1932, suggested its use as a test in routine life insurance examinations. Gallagher,⁸ in 1934, advocated its use as a valuable aid in routine yearly health examinations of school children. J. B. Stokes²¹ suggested that the sedimentation rate may replace the Schilling index as an indication

of pathologic activity. Westergren²³ advocated its use in the prognosis and therapy of diseases. Agnor,¹ in 1940, advocated its use as a routine diagnostic procedure and believed it to be of value equal to the Wassermann reaction, blood count, and urinalysis. Shillito, Chamberlin and Levy,¹⁹ in 1942, claim the sedimentation rate to be the most important aid in the diagnosis of coronary occlusion.

Weil, Smith, King and Wootton,²² however, believe the usefulness of the sedimentation rate has been overrated in arthritis. Peterman¹⁵ regards one determination as of little value in diagnosis or prognosis, but serial determinations of great value in following the course of diseases.

There has been much debate as to the necessity of correcting results in the presence of anemia. Rourke and Ernstene,¹⁷ in 1930, finding an inverse relationship between the rate of settling and the volume percentage of the red blood cells, plotted the sedimentation curves of blood from the same individual after the cell volume % was adjusted to different levels. From these, they derived curves for correcting the sedimentation rate for the volume percentage of packed red blood cells. Bouton,² in 1938, stated that correction of the sedimentation rate for anemia is unnecessary, but that the unmodified curve is a valuable diagnostic aid when correlated with other findings. Cutler, Park and Herr,⁵ in 1935, found the rate of erythrocyte sedimentation to be directly dependent upon the size of the rouleaux formed, and that the rate of sedimentation was a property of the plasma rather than of the cells. They divided the sedimentation phenomenon into the phases of aggregation, settling, and packing; and pointed out that the second or settling phase is the important one. The anemia factor was prominent only in the terminal or packing phase. They found that blood which had a normal or slow settling rate showed only a slight increase in the rate of settling and formed only slightly larger rouleaux after the removal of portions of the cells.

Of other general considerations, agreement is unanimous: 1, "that the glassware must be clean;" 2, the tube must be absolutely vertical; 3, the test must be done within 3 hours after collection of the blood; 4, the temperature should be between 20 and 25° C.; 5, the tubes must be of a uniform and equal diameter, greater than 2.5 mm.

The anticoagulant used by Cutler⁵ is sodium citrate 0.1 cc. of 3% solution per 0.9 cc. of blood. The dry mixture of 4 mg. of potassium oxalate and 6 mg. ammonium oxalate is advocated by Heller and Paul¹⁰ as being almost similar to heparin in its action.

The components of plasma which govern the rate of erythrocyte sedimentation have been investigated by many authors. Ham and Curtis⁹ found a direct correlation between the blood fibrinogen content and the rate of sedimentation. There is a slight relation between the blood cholesterol and the sedimentation rate.

There are 3 techniques in use. 1, The Linzenmeier¹³ method, in which the time required for the erythrocytes to settle 18 mm. is determined. 2, The Westergren²⁴ method, in which the millimeters of sedimentation in 1 hour is determined. 3, The Cutler⁶ method in which the level of the settling erythrocytes is read at 5-minute intervals for 1 hour and recorded graphically.

The accuracy of the test in indicating the presence of tissue destruction has been reported to be very high. In Cutler's⁴ series of 5000 cases, there was a discrepancy between the sedimentation rate and the clinical status of the patient in only 5 cases. Yates and Davidow²⁵ describe an accuracy of 91.4% in 6000 tests. Polak and Tollefson¹⁶ state: "The sedimentation test never lies."

In individual diseases, the sedimentation rate has been described as being increased in tuberculosis, rheumatic fever, pelvic inflammatory disease, coronary infarction, active syphilis, gonorrheal and atrophic arthritis, malignancy, hyperthyroidism, and any process in which tissue destruction or chronic infection exists.

It has been described as being questionably increased in chronic sinusitis, dental infection, and tonsillitis.¹²

It has been found to be increased in patients with long-standing diabetes,¹¹ but not in older patients with no disease.¹⁴

Method. Our series of records has been reviewed in an attempt to determine the predictability and usefulness of the sedimentation test as used on the medical service of the University Hospital.

The records of 1000 consecutive patients, on whom a sedimentation rate was determined, were reviewed. In order to obtain this number, we reviewed the records of 3019 patients admitted during the period of August 1, 1939 to April 1, 1942. Since many patients were admitted more than one time during the period surveyed and were counted but once in the series, the sedimentation rate is being performed in approximately 40% of our patients.

The number of rates performed on each patient varied from 1 to 12.

The sedimentation rate was determined by one of two techniques: 1, 64.3% were obtained by the original Cutler⁶ technique; 2, 35.7% were determined by a modified Rourke-Ernstene¹⁷ technique using the oxalate mixture of Heller and Paul¹⁰ as an anti-coagulant, with a correction for the packed cell volume by use of a nomogram constructed by Dr. Richard Singer and Dr. Nelson K. Ordway²⁰ from the curves of Rourke and Ernstene.

These patients were grouped according to age with extremes of 11 and 85 years. Two hundred forty-three were between 11 and 30 years, 208 from 31 to 40, 203 were from 41 to 50, 187 from 51 to 60, and 159 were over 61.

The records of these patients were analyzed and a prediction of the character of the sedimentation rate was made from the history and physical examination. This prediction was whether the rate would be increased or normal. The sedimentation rate was then compared with the final diagnosis and a decision made as to its help in therapy in each instance.

From this survey we were able to predict the nature of the sedimentation rate in 943 cases (Table 1). Of this number, in 173 cases (Table 2) the sedimentation rate was not only predictable, but confirmatory in regard to the final diagnosis, and also acted as

a guide to therapy in the case. In 770 cases, it was both predictable and confirmatory, but had no effect on the treatment of the patient.

TABLE 1.—PREDICTABILITY OF THE CHARACTER OF THE SEDIMENTATION RATE (INCREASED OR NORMAL)

	No. of cases	%
Sedimentation rate predictable	943	94.3
Sedimentation rate not predictable	57	5.7
Total	1000	100.0

TABLE 2.—USEFULNESS OF THE SEDIMENTATION RATE

Predictable	Confirmatory	Guide to therapy	No. of cases
+	+	+	173
+	+	0	770
0	0	0	57
Total			1000

In 173 cases, the rate was predictable, confirmatory and a guide to therapy. In 770, it was predictable, confirmatory, but had no influence on therapy. In 57, it was unpredictable and of unknown significance.

TABLE 3.—SEDIMENTATION RATE NOT PREDICTABLE

	No. of cases
Cause for discrepancy found on re-analysis	41
No cause for discrepancy found	16
Total	57

In 57 cases (Table 3), the sedimentation rate was not predictable and had an unknown significance. The records of this group were reviewed meticulously and in 39 of them some factor, such as chronic alveolar abscess, chronic purulent sinusitis, chronic cervicitis, or syphilis, was discovered and explained the discrepancy. In 2 additional cases of coronary occlusion normal sedimentation rates were reported, but they had not been determined until the 4th week of the disease.

In the remaining 16 cases (1.6%) no explanation could be found for the discrepancy between the sedimentation rate and the clinical diagnosis or evaluation of the patient. This corresponds with the range of accuracy in series reported previously.

An example is given of a patient in whom an unexplained rapid sedimentation rate was reported.

CASE 1. A 45-year-old white female, was seen in our medical clinic and referred to the ward. She complained of pain in her lumbo-sacral region for 10 years. This pain became worse during damp weather. It was aggravated by exercise, especially on leaning forward. It was relieved by rest. The remainder of the systemic review of symptoms was negative. Physical examination revealed slightly enlarged and apparently non-infected tonsils, scoliosis of her dorsal spine, and bilateral Hallux valgus. Her body temperature was normal.

Laboratory studies showed 4,300,000 red blood cells, 84% (Sahli) hemoglobin with 7650 white cells and a normal differential. Blood urea nitrogen

was 9 mg. per 100 cc.; blood sugar was 87 mg. per 100 cc. Urinalysis was negative. Blood Wassermann reaction was negative.

Roentgen ray films of her spine were normal except for slight scoliosis. Her chest was clear.

Sedimentation was 85 mm. per hour (corrected for anemia with a hematocrit of 43% packed cell volume).

Our statistics were then reevaluated and those cases of psychoneurosis, hypochondriasis, and the anxiety state where a normal sedimentation rate was of assistance in ruling out a morbid process were included in the group in which the sedimentation rate was of help to us. There were 64 such cases. This gives us a final figure of 237 cases in which the sedimentation rate was of assistance in the diagnosis and management of the case and 763 in which it was of no value (Table 4).

TABLE 4.—EVALUATION OF ASSISTANCE GIVEN BY THE SEDIMENTATION RATE IN DIAGNOSIS OR MANAGEMENT OF CASE

Evaluation	No. of cases
Helped	237
No help	763

We have confirmed the reports already in the literature and agree that the test is of value in determining the presence and extent of tissue destruction, the systemic reaction to a disease process, and as a lead for the need of further investigation in an otherwise healthy individual. We believe serial tests in patients with chronic types of disease to be of benefit in following the course of the process. Single tests are of value only in patients whose history and physical examination disclose no definite disease process and the test is, therefore, used as a lead to further investigation.

Summary. 1. In the records of 1000 patients on whom the sedimentation rate was determined, it was predictable in 943 cases. In 173, it was not only predictable, but confirmatory in regard to the final diagnosis, and of help in the treatment of the case. In 770, it was both predictable and confirmatory in regard to the final diagnosis, but of no help in therapy. The rate was not predictable in 57 cases, but on re-analysis of these records, an explanation of the unexpected rate was discovered in 41.

2. In 16 (1.6%), no explanation was found.

3. Including those cases in which a normal rate was of assistance in diagnosis, the sedimentation rate helped in our management of the case in 237 and was of no help in 763.

Conclusions. We believe serial determinations of the sedimentation rate to be of value in following the course of such diseases as rheumatic infection, tuberculosis, coronary occlusion and arthritis.

We believe single tests to be of little or no value, except in patients who, in the absence of evidences of organic lesions, are suspected of having only a functional disease. In these patients, an increased sedimentation rate suggests the presence of a morbid process and makes further investigation mandatory.

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THROMBOCYTOPENIC PURPURA CAUSED BY SULFONAMIDE DRUGS

A REPORT OF 3 CASES

By L. WHITTINGTON GORHAM, M.D.

PROFESSOR OF MEDICINE

SIMON PROPP, M.D.

ASSISTANT PROFESSOR OF MEDICINE

JOSEPH L. SCHWIND, PH.D.

ASSOCIATE PROFESSOR OF ANATOMY

AND

DAVID R. CLIMENKO, M.D., PH.D.

INSTRUCTOR IN MEDICINE

ALBANY MEDICAL COLLEGE, UNION UNIVERSITY, ALBANY, N. Y.

(From the Departments of Medicine and Anatomy)

THE brilliant therapeutic results which have been obtained with sulfanilamide and its derivatives in the treatment of various infections have led to a constantly increasing clinical use of this group of drugs. Since their introduction there have been numerous reports of various toxic effects. Destructive action upon the blood and blood forming organs has been noted in some cases, with

production of hemolytic anemia, granulocytopenia and leukemoid reaction, but thus far only 4 reports of thrombocytopenic purpura have appeared in the literature.

Perrin Long⁷ and his associates have reviewed the toxic manifestation of the sulfonamides in a group of 1588 patients. Of these, 1000 received sulfanilamide, 297 sulfapyridine, and 291 sulfathiazole. Regarding the occurrence of hemorrhagic phenomena these authors state that "purpura hemorrhagica has not been seen in any of our cases, but it has been reported as occurring in the course of therapy with sulfanilamide and sulfapyridine."

Finland,³ who has had a very wide experience with the sulfonamide group of drugs at the Boston City Hospital, reports that he has seen no instances of thrombocytopenic purpura following their use.

Markel and Rike⁸ described the first case of secondary purpura hemorrhagica following the administration of sulfanilamide.

CASE A. A 59-year-old man had a resection of the bowel for lymphosarcoma of the terminal ileum with partial obstruction. Ten days after operation, because of cystitis, sulfanilamide therapy was begun. Thirty grains were given on the first, and 15 gr. on the second day, when oozing of blood from the operative wound was noted. A total of 7 gm. was given in 4 days, when it was stopped. Bleeding from the wound continued, bloody expectoration occurred, and blood was found in the urine. A 500 cc. transfusion of citrated blood was given. At this time the bleeding time was prolonged, the coagulation time was within normal limits, and the clot failed to retract after 12 hours. The platelet count was 180,000. A second transfusion was given, but the patient died on the following day, one week after the beginning of sulfanilamide therapy. The autopsy showed hemorrhage into the tissues surrounding the entero-enterostomy, in the abdominal incision, and into the right renal pelvis. The bone marrow presented a normal picture.

Russell and Page¹² reported two examples of thrombocytopenic purpura due to sulfapyridine.

CASE B. A 41-year-old negro with pulmonary tuberculosis developed pneumonia of the left lower lobe. During the first 10 days in the hospital he received 4.5 gm. daily, a total dose of 45 gm. Ten days after admission he developed hemoptysis and recurrent epistaxis. The drug was discontinued. On the 11th day he showed a generalized purpura involving the entire body and the epistaxis and hemoptysis became continuous. Oozing of blood from the gums also appeared, as did profuse bleeding from the mucous membranes of the mouth. The platelet count was 34,000. The bleeding, coagulation, and clot retraction times were not determined. The diagnosis of thrombocytopenic purpura was made. The patient received 4 transfusions, a total of 1750 cc. of blood. Although he continued to have purpuric manifestations for 5 days after the first transfusion eventual recovery occurred.

CASE C. A 60-year-old Italian male, had a pneumonia of the left lower lobe of 3 days' duration. He was given 18 gm. of sulfapyridine within the next 4 days. The drug was discontinued on the 4th day because of hematuria. This was followed by a rise in temperature. During the next 3 days he received an additional 5 gm. of sulfapyridine. The patient then devel-

oped epistaxis which lasted 6 hours. The following day he showed purpuric manifestations in the skin, face, and extremities. The bleeding from the nose continued. On the next day he developed bleeding from the gums and mucous membranes of the mouth. Large ecchymotic areas appeared on the skin, in the throat, and on the extremities. The patient began to pass large tarry stools. He received 3 transfusions totaling 1700 cc. of blood with little effect upon the bleeding. No platelets were seen in the smear, although they were apparently normal on admission. The bleeding time was 184 minutes; the coagulation time was 9 minutes. No test for clot retraction was recorded. Bone marrow biopsy did not show any significant changes. There was a moderate increase in the megakaryocytes and a definite increase in the nucleated red blood cells. The latter was believed to be due to the response of the bone marrow to blood loss. The patient died 14 days after admission. Permission for an autopsy could not be obtained.

CASE D was reported by Goldbloom, Greenwald, and Reinstein.⁵ The patient was a 50-year-old woman who was admitted to the hospital with a clinical diagnosis of pneumonia. Physical examination revealed marked dullness, increased tactile and vocal fremitus, and fine crepitant râles over the right, middle, and lower lobes. The clinical diagnosis was substantiated by Roentgen ray. Sixty grains (4 gm.) of sulfapyridine had been administered daily for 5 days before admission. After admission 90 gr. (6 gm.) were administered daily for 2 days and her temperature declined from 103° F. on admission to 98° F. on the 3d day, at which time bright red blood was expectorated. Hemorrhagic papillomatous masses appeared in the buccal mucosa; there were elevated red papillae at the borders of the tongue, hemorrhage into the gingival tissue of the lower jaw, and moderate vaginal bleeding. That night a generalized rash appeared, and there was a hemorrhage into the left sclera. Sulfapyridine was discontinued after 32 gm. had been given in 8 days. A blood transfusion was given with 500 cc. of saline solution and coagmine (thromboplastin). The following day the patient showed marked pallor, and purpura appeared in scattered patches over the trunk and extremities, accompanied by a large ecchymotic area over the left thigh. The patient eventually recovered.

Rosenfeld and Feldman¹¹ have recently reported a case due to sulfathiazole.

CASE E, 37-year-old male, entered the hospital with unilateral ureteral calculus, ureteral obstruction, and pyelonephritis. The temperature on admission was 104.4° F. Sulfathiazole was administered, 1 gm. on the day of admission, and 4 gm. the next day. The temperature fell to 100.5° F. The following day, after another 0.5 gm. had been administered, a hemorrhagic state became manifest and the patient's temperature rose to 103° F. There was profuse bleeding from the nose and gums, and hematuria appeared. Numerous hemorrhagic vesicles developed on the tongue, lips and buccal mucosa, and there were many petechiae on the skin. The patient showed extremely marked pallor. Platelets were absent from smears of the peripheral blood, and the tourniquet test was positive. Sulfathiazole was discontinued at the first appearance of bleeding, and after the lapse of 3 days the hemorrhagic phenomena began to subside so that at the end of 2 more days, the vesicles and petechiae had disappeared from the skin and mucous membranes, and the pulse and temperature were normal. Platelets reappeared in the peripheral blood, and the tourniquet test was now negative. Ten days later, following the removal of the kidney stone, this patient was given 15 gm. of sulfathiazole in 5 days as a prophylactic measure without recurrence of any hemorrhagic phenomena.

TABLE 1.—RECORDED

[illegible]

In addition to the 5 published cases which have been summarized, we wish to report 3 more examples. The first is of special interest because the secondary type of thrombocytopenic purpura which followed the administration of neoprontosil and sulfanilamide was at first confused with primary purpura hemorrhagica. The third case is the first instance, as far as we know, in which sulfadiazine, the least toxic of the sulfonamides, was responsible for purpura and death. A comparison of the essential features of 8 published cases, including the 3 hereafter to be described, is given in Table 1.

CASE 1. (Albany Hospital, No. 63,654.) A 23-year-old white, married, garage worker, born in the United States, of Lithuanian parents, on May 24, 1941, developed a sore throat, laryngitis and coryza for which he was treated by his local physician. His temperature reached 104° F. The patient received one 0.5 gm. tablet of neoprontosil every 4 hours for 8 doses (total 4 gm.) but on the following day was nauseated and vomited so that his physician stopped the drug and prescribed sulfanilamide. He was given one 0.5 gm. tablet every 4 hours for 6 doses (total 3 gm.). Medication was then discontinued because of the appearance of nosebleed and oozing from the gums. On June 2 the blood count showed red cells 5,510,000, hemoglobin 115%, white blood cells 7900 (75 neutrophils), platelets 90,000.

On June 3, 1941, he was admitted to his local hospital. Physical examination revealed numerous ecchymotic areas in the mucous membranes of the mouth, especially about the lower lip. There were also many petechiae scattered over the flexor surfaces of the forearms in the region of the elbows and over the back. One large ecchymosis approximately 3 inches in diameter was present on the outer aspect of the upper right arm, and a few small ecchymoses around the anus. A repetition of the blood count showed the same findings as on June 2. The clotting time was 2.5 minutes, bleeding time 8 minutes, platelet count 77,000, and clot retraction very slight after 18 hours. A test for sulfanilamide in the blood was negative. The stool showed a 4+ positive reaction for blood. On June 6, the platelet count was 105,000; bleeding time 7 minutes, 45 seconds; and clot retraction very slight after 22 hours. On June 9, the platelet count was 106,000; on June 12, 134,000. A tentative diagnosis of essential thrombocytopenic purpura was made and the question of splenectomy considered. The patient was discharged from the hospital June 10 and for the next week remained at home where the bleeding from the gums continued and fresh petechiae appeared.

On June 17, 1941, he was admitted to the Albany Hospital. A review of the past history showed no operations and no accidents. In 1918, he had influenza. In 1939, he had an attack of tonsillitis followed by an erythematous rash at which time the question of scarlet fever was raised. He was given no specific medication for this infection. He had never before received any of the sulfonamide group of drugs to his knowledge. A review of systems was negative. Venereal disease was denied. The family history was negative.

Physical examination revealed a powerfully built, well nourished, white male, lying quietly in bed, who did not appear acutely ill. The temperature was 97.5° F., pulse 65, and respirations 18. He occasionally spat out small quantities of bloody saliva. Petechial hemorrhages were widespread over his forehead, eyelids, in the conjunctivae, over the forearms, in the left subclavicular region, and over the back and legs. Ecchymoses, 3 inches in diameter were present over the biceps muscle of the right arm and over the right patella. The pupils were equal and reacted to light. The ears and nose were negative. The lips and oral mucous membranes were of good

color. Blood was oozing from the gums. The pharynx was negative. The thyroid was not enlarged. There was no general glandular enlargement. The chest was well formed; the lungs were clear; the heart was normal. The blood pressure was 115 systolic and 75 diastolic. The spleen and liver were not palpable and the abdomen was entirely negative. The genitalia were normal. The extremities were normal. The knee- and ankle-jerks were present. The tourniquet test for capillary resistance was positive.

Laboratory Data (June 18). Urine, negative; blood non-protein nitrogen, 36 mg. 100 cc.; red blood count, 4,600,000; hemoglobin, 14 gm. (85%—Hayden-Hauser); color index, 0.9; white blood cells, 8100; differential count: segmented neutrophils 41%, band forms 22%, metamyelocytes 1%, myelocytes 1%, eosinophils 3%, monocytes 8%, lymphocytes 24%; platelets were rare in the blood smear; platelet count 36,000 by the indirect method; bleeding time over 9 minutes; clotting time (venous blood) 9 minutes, 30 seconds; clot retraction incomplete after 36 hours; reticulocyte count 3%; blood type, Landsteiner O; stool tarry, with positive guaiac test.

On June 20 the patient was given a 500 cc. transfusion of citrated blood. The temperature rose to 100° F., but there was no other reaction.

Sternal puncture (June 21). Smears from the aspirated fluid (Wright's stain) showed an actively functioning marrow with a normal differential count. Platelets were present but few. There was no evidence of leukemia or aplastic anemia. The findings were consistent with a diagnosis of thrombocytopenic purpura.

On June 22, 2 days after the transfusion, the bleeding time was 5 minutes; clotting time (venous blood) 7 minutes, 15 seconds; and clot retraction complete after 12 hours. The prothrombin time, on the following day was: patient 38 seconds, control 32 seconds, 88% of normal.

By June 24 the platelet count had risen to 415,000 (indirect method), and the other blood findings had also returned to normal. During the succeeding 2 days there was no further bleeding from the gums, no new petechiae formed, and the older hemorrhages began to fade and disappear. The test for capillary resistance was negative. The patient was discharged from the hospital June 26, 1941.

Subsequently he had no further hemorrhagic manifestations, and on August 12, 1941, a complete follow-up examination of the patient was entirely normal.

CASE 2.* A 62-year-old white male, was treated for pneumonia with sulfapyridine. His illness began March 1, 1940, as an acute respiratory infection. On March 3 his temperature was 103° F., respirations 30 per minute, and pulse 110. There were numerous râles in the lower left lobe, and the patient coughed almost continuously but could raise no sputum. He was given 3 gm. of sulfapyridine, repeated after 4 hours, and thereafter 1 gm. every 4 hours. The temperature came down to normal within 24 hours, and at the end of the 3d day of treatment, when the patient had received 18 gm. of the drug, medication was discontinued. There was little nausea and no vomiting from the medication. The temperature remained normal for 3 days until March 8, when it jumped to 101° F. Sulfapyridine was started again, 1 gm. every 4 hours. The temperature again dropped to normal in 24 hours, but the drug was continued. On March 9, crystals of sulfapyridine appeared in the urine. On March 12 the patient passed bloody urine and the drug was discontinued. A total of 18 gm. over a period of 3 days had been given, and then after an interval of 3 days, 30 gm. were administered in 5 days. On the following day, the patient's color was good, he did not appear ill, nor did he complain of any pain. Examination of the lungs revealed a patch of consolidation in the

* We are indebted to Dr. S. L. Cash and to Dr. Russell L. Cecil of New York for permission to report this case.

left lower lobe. There was no tenderness over the kidneys and no pain in the back. The patient received 1000 cc. of saline solution intravenously, and fluids were forced by mouth. On March 14 he began to bleed from the nose, mouth and lower bowel and large purpuric spots appeared all over the body.

Laboratory Data (March 15). Red blood cells, 3,270,000; hemoglobin, 49% (Klett-Newcomber 8.3 gm.); white blood cells, 11,800; blood platelets—practically none seen in stained smear; bleeding time, 3 minutes (Duke's method); coagulation time, 4.5 minutes (capillary blood); blood non-protein nitrogen, 79.3 mg. per 100 cc. A diagnosis of purpura hemorrhagica was made, and while preparations were being made for a blood transfusion the patient suddenly became very much worse and died, March 16. Postmortem examination of the embalmed body showed multiple purpuric hemorrhages on the chest, back, extremities and on the surface of the intestines and kidneys. The latter organs were slightly enlarged and on sectioning showed extensive submucosal and interstitial hemorrhage in the papillæ, calices, and pelves. The hemorrhages extended into the ureter, and extravasated blood was found in the lumen of the pelves and ureters. Microscopic examination confirmed the gross findings. Acetyl-sulfapyridine crystals were not found; the other organs were not examined.

CASE 3.* A 60-year-old woman (N. Y. Hosp., No. 300468) was first treated by Russell traction for a fracture of the left hip. Failure to obtain satisfactory reduction led to fixation of the fragments with Moore pins 7 days after her admission to the hospital. She was a known diabetic, but her diabetes was readily controlled. Four days after the insertion of the Moore pins, and the 3d day after the patient had been allowed up in a chair, her temperature rose to 39.2° C., and there was induration of the wound. The wound was opened and a serous material evacuated which on culture revealed non-hemolytic *Staphylococcus aureus*. Sulfadiazine therapy was instituted. She received 6 gm. the first day, 3 gm. the second, and 4 gm. daily for the next 4 days. Over a period of 6 days she received 25 gm. of sulfadiazine, during which time daily blood counts revealed no depression of the white blood cells, but no platelet counts were done. On the 6th day the patient developed severe epistaxis, followed by bleeding from the gums and urinary tract. The blood level of the drug was at this time 3.6 mg.

Laboratory Data. Red blood cells, 3,100,000; white blood cells, 15,000; differential count—segmented neutrophils 34, band forms 49, monocytes 3, lymphocytes 14. No platelets were seen in the smears. Clotting time was 3 minutes, bleeding time 20 minutes.

Diagnosis. Thrombocytopenic purpura. Sulfadiazine was discontinued, and the patient given multiple small transfusions and supportive therapy. In spite of this she continued to bleed from the nasal mucous membrane, urinary tract, gastro-intestinal tract, and vagina. The patient died 8 days after the institution of sulfadiazine therapy, 2 days after the appearance of purpuric manifestations, having received 25 gm. of the drug in 6 days.

Postmortem Examination. Purpura hemorrhagica (medicamentosa, sulfadiazine) with hemorrhage into the wound, joints, serous surfaces, lungs, stomach, renal pelves, bladder, dura, brain and wall of the third ventricle.

Comment. A total of 8 cases of secondary thrombocytopenic purpura (including the 3 herein described) following the use of sulfonamide drugs have now been reported. There were 4 deaths.

* We are indebted to Dr. Norman S. Plummer of New York for the privilege of including this case in our series. The patient was studied on the Surgical and Chemotherapy Services of the New York Hospital.

Fatal purpura has been caused by: sulfanilamide, sulfapyridine, and sulfadiazine. The one reported case of purpura following the use of sulfathiazole recovered. Purpura hemorrhagica must now be generally recognized as a possible serious, although infrequent, complication of sulfonamide therapy. The drug should be stopped at once when it appears. The number of blood platelets should be noted when the blood is being checked for possible granulocytopenia during sulfonamide therapy.

A study of the 4 fatal cases thus far reported shows that in at least 2 instances and possibly 3 the drug was continued for 24 to 48 hours after petechial hemorrhages or bleeding had occurred. In the 4 patients who recovered, the drug was stopped on the first appearance of hemorrhagic manifestations. This point is of great practical importance. Since thrombocytopenia precedes the appearance of purpura it is obvious that the detection of a reduction of blood platelets in the blood smear would be of even greater value as a danger signal than the finding of a few petechiæ or slight hemorrhage. The sooner the drug is stopped in one of these sulfonamide sensitive patients, the better appears to be his chance for recovery.

The bone marrow shows no significant change in these cases. Needless to say, this secondary drug purpura must be distinguished from primary thrombocytopenic purpura. The amount of drug necessary to produce purpura, is, as can be seen in Table 1, extremely variable. Death occurred with as little as 7 gm. It is interesting to note that in the case reported by Rosenfeld and Feldman purpura appeared after the administration of 5.5 gm. of sulfathiazole, but after recovery had taken place 15 more grams of the drug were given to the same patient without any untoward effect.

At the present time, no definite statement can be made to explain the blood dyscrasias which occur in certain individuals as a result of the administration of the sulfonamides. The similarity in chemical structure however, between this group of drugs, and such known hematotoxic agents as benzol and aniline, makes the similarity in the clinical manifestations of their toxic reactions all the more striking. When it is realized that the organism handles these 2 types of substances in a fundamentally similar manner; that they are closely related to one another from a chemical point of view; and that they are capable of producing identical pathologic lesions insofar as the hematopoietic system is concerned, then it is reasonable to assume that the production of blood dyscrasias by the 2 types of substances involves the same fundamental mechanism (Fig. 1).

The structural relationship between benzol, aniline, and the sulfonamides calls for no comment. It is clearly brought out by inspection of the structural formulæ. In the case of sulfapyridine,

sulfathiazole and sulfadiazine, the "R" in the formula represents a heterocyclic ring (Fig. 1).

In the body, aniline is converted to phenylhydroxyl amine and then to p-amino phenol. This oxidation compound is excreted in combination with sulfate as an ethereal sulfate. A definite increase in ethereal sulfate output is characteristic of benzol and aniline poisonings, and one of the first clinical manifestations of intoxication with such substances is the lowering of the ratio of excreted inorganic sulfur to total sulfur in the urine.

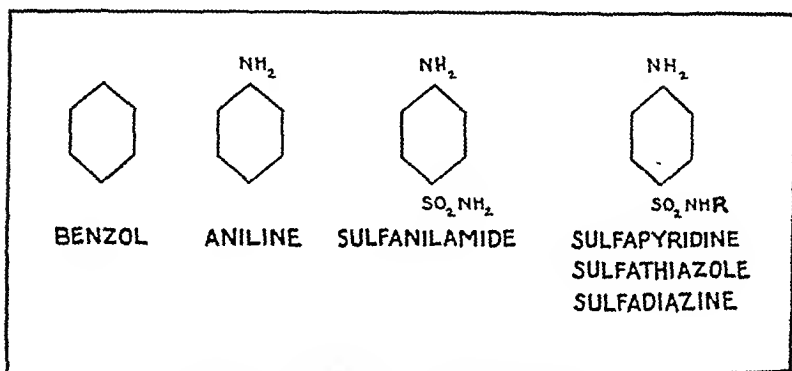


Fig. 1.—Structural formulas of the sulfonamides.

Both Fuller⁴ and Marshall,⁹ in describing the metabolism of the sulfonamides, have pointed out that these compounds are either acetylated or excreted unchanged. This is undoubtedly true for the major portion of these substances, and in some individuals, may account for all of the drug administered. However, it may be shown in experimental animals that the administration of a single dose of sulfapyridine is followed by a marked increase in the quantity of ethereal sulfate excreted. This is associated with a concomitant lowering of the ratio of inorganic sulfur to total sulfur. Figure 2 shows the results of such an experiment. A dog, maintained on a normal fixed diet, was allowed to come to equilibrium insofar as sulfur metabolism was concerned. After this had been established a single dose of sulfapyridine (1000 mg./kg., per oreum) was administered and sulfur metabolism followed. The maximal increase in ethereal sulfate output occurred on the day following the administration of the drug, and the concentration rapidly returned toward its initial basal level (Fig. 2).

This increase in ethereal sulfate excretion may be the result of either of two mechanisms: *A*, a derangement of the endogenous protein metabolism with the resulting increased formation of such catabolites as indol, etc., which are excreted as ethereal sulfates; or, *B*, the oxidation of a portion of the sulfapyridine which had been administered and the conjugation of this oxidized compound with sulfate to form an ethereal sulfate.

Of these two possibilities, the second is the more probable, since there is indirect evidence that the administration of large doses of sulfonamides do not produce any demonstrable change in liver function.¹ Furthermore, there is the direct evidence of James⁶ who has been able to isolate a series of oxidation products of sulfanilamide, which are analogous to the known oxidation products of aniline, from the urines of patients receiving therapeutic doses of the drug. He suggested that some of the toxic effects noticed by clinicians might be due to these oxidation products and pointed out that both the p-aminophenol and the hydroxylamine compounds, in their unconjugated form, are capable of producing degenerative blood changes.

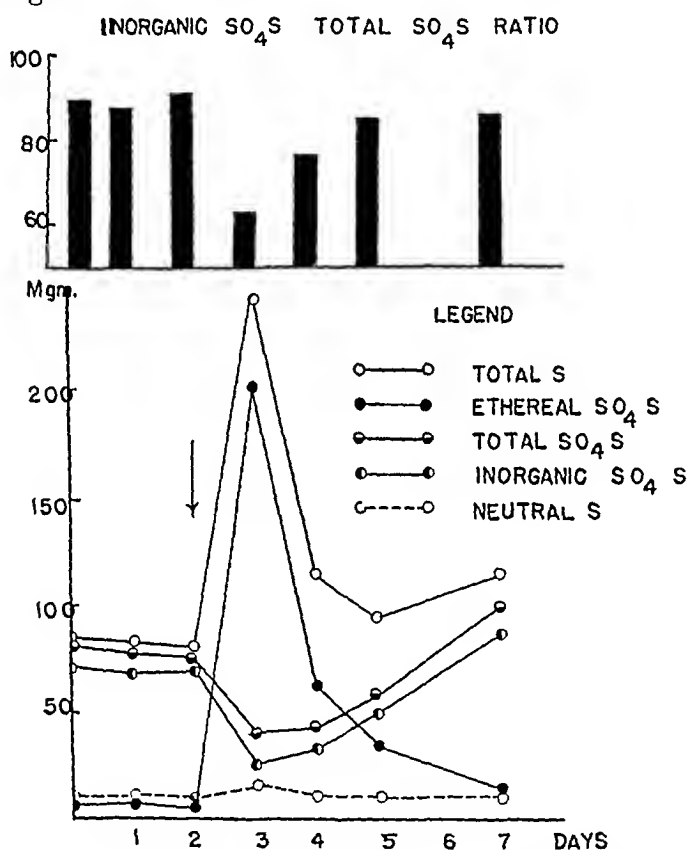


FIG. 2.—The effect of sulfapyridine on sulfur metabolism.

In addition to possessing a potential toxic action on the hematopoietic mechanism, all of these compounds (benzol, aniline and the sulfonamides) have a direct effect on the cells of the peripheral circulation. Neither benzol nor aniline are hemolytic substances; *i. e.*, saturated solutions of these substances in isotonic saline will not produce hemolysis of washed red cells. However, they will accelerate the rate at which hemolysis occurs in the presence of a known lysin. If one establishes the time required for the production of complete hemolysis of a suspension of cells by a known concentration of lysin, and then alters the system by the addition of small

quantities of benzol or aniline, it will be observed that the time required for complete hemolysis by the same quantity of lysis is materially diminished. This acceleration of the lytic action is also a property of the sulfonamides and may be demonstrated *in vivo* as well as *in vitro*. The property of accelerating the hemolytic process may account for the hemolytic anemias encountered as a result of the administration of the sulfonamides. Rimington¹⁰ was able to show a marked increase in the hematoporphyrin excretion of rats receiving sulfapyridine. We have administered sulfathiazole to dogs and have noted this same increase in pigment excretion in the urine. The peripheral blood has shown a normal picture. Erf and MacLeod² reported increased urobilinogen outputs in patients receiving sulfapyridine and manifesting the clinical picture of hemolytic anemia.

The multiplicity of the clinical manifestations of blood dyscrasias resulting from the administration of the sulfonamides is duplicated by benzol and aniline intoxication. The effect may be on the cells of the peripheral circulation or on any or all of the series of blood cells produced in the bone marrow. Thus following the administration of sulfonamides, as well as in benzol or aniline intoxication, there may occur granulocytopenia, hemolytic anemia, leukemoid reaction, thrombocytopenic purpura and possibly aplastic anemia. To our knowledge no instance of aplastic anemia following sulfonamide therapy has been reported, although we believe that such cases may occur and be recognized in the future.

Summary and Conclusions. 1. Three new cases of thrombocytopenic purpura following the use of sulfonamide drugs are reported and 5 previously published cases are reviewed. Table 1 contains a summary of these 8 cases.

2. In our series of 3 cases, one followed the administration of neoprontosil and sulfanilamide to the same patient. Recovery occurred. The other two examples followed the administration of sulfapyridine and sulfadiazine respectively. Both of these patients died.

3. All of the well-known sulfonamide compounds thus far generally used have produced purpura in susceptible individuals. Sulfanilamide, sulfapyridine, and sulfadiazine, have caused death. The one patient who is reported to have had purpura following sulfathiazole recovered.

4. The total amount of drug administered in the cases reported has varied from as little as 5.5 gm. in 3 days to 48 gm. over a period of 11 days. This wide variation in the amount necessary to produce a toxic effect indicates a great difference in individual susceptibility. In one patient who recovered, the same drug was given a short time subsequently, with no untoward effect.

5. Purpura should be generally recognized as a possible though infrequent complication of sulfonamide drug therapy. The mortality

has thus far been very high—50% in the 8 cases reported, so that the seriousness of this complication should be emphasized.

6. The study shows that the sooner sulfonamides are stopped after the appearance of purpura the better the prognosis for recovery of the patient.

7. When examining blood smears from patients receiving sulfonamide therapy, for possible granulocytopenia, a note as to the number of platelets present should always be made. Thrombocytopenia precedes the signs of purpura, and early observation of platelet reduction may prove life saving.

8. The striking similarity between the clinical signs of the hematotoxic action of benzol and aniline on the one hand, and of the sulfonamides on the other, has been emphasized. When it is realized that the organism reacts in a fundamentally similar manner after the ingestion of these two types of substances, that their chemical structure is closely related, and that they are capable of producing identical pathologic lesions in the bone marrow, and in the peripheral blood, then it is reasonable to assume that the production of various blood dyscrasias by the two types of substances involves the same fundamental mechanism.

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THE EFFECT OF STORAGE AT VARIOUS TEMPERATURES ON THE PROTHROMBIN CLOTTING TIME OF HUMAN PLASMA

By ROBERT C. PAGE, M.D.

AND

EDWIN J. DE BEER, PH.D.

NEW YORK, N. Y.

(From the Chemical Laboratory of the Department of Surgery, College of Physicians and Surgeons, Columbia University and Presbyterian Hospital, and The Burroughs Wellcome & Co. [U.S.A.] Experimental Research Laboratories, Tuckahoe, N. Y.)

We have been impressed by the change in prothrombin clotting time of human plasma when it is allowed to stand at room temperature. Obviously this is of considerable clinical importance in

interpreting a prothrombin clotting time. In an earlier publication² we stated that if plasma is allowed to stand at room temperature the prothrombin clotting time is usually increased and consequently we performed the test as soon as possible after obtaining the blood. Witts and Hobson⁵ have reported that oxalated plasma is not stable for much longer than an hour at room temperature, however, if put into a refrigerator as soon as possible after venipuncture the plasma will keep its clotting time unchanged for at least 24 hours. Because of the above observations we were prompted to carry out the following study on the effect of different temperatures on the prothrombin clotting time of human plasma.

Method. Samples of venous blood from normal individuals, and from obese and diabetic patients attending an out-patient clinic, were centrifuged and the plasma was divided into 3 portions. One was stored in an incubator at 38° C., another at room temperature (about 23° C.), and the third in the refrigerator at approximately 5° C.

Ten mg. of potassium oxalate were mixed with 4.5 cc. of blood in a centrifuge tube. The blood was centrifuged at 1500 r.p.m. for 5 minutes, and the oxalated plasma was pipetted off. The test was performed as follows: 0.2 cc. of oxalated plasma was pipetted into a small test-tube (75 x 10 mm.) and 0.2 cc. of Russell viper venom,* 1:10,000 solution, was added. Calcium chloride solution (1.11 gm. anhydrous calcium chloride per 100 cc.), 0.2 cc., was then added, and the stopwatch immediately started. The tube was agitated for 10 to 15 seconds and tilted until separate discrete fibrin particles could be seen. This was taken as the end-point. The prothrombin clotting time in normal individuals using Russell viper venom has been found to be 20.76 ± 2.32 sec.² and 19.5 ± 2.9 sec.³

Results. It was not always possible to make determinations exactly at 1, 2, 3 and 4 hours after the blood sample was obtained, therefore the prothrombin clotting times were plotted against the times at which the determinations were made for each of the blood samples involved. When necessary, therefore, the required prothrombin clotting times for a given hour were read from the graph.

TABLE 1.—PROTHROMBIN CLOTTING TIMES IN SECONDS FOR SAMPLES OF PLASMA STORED FOR GIVEN PERIODS OF TIME AT DIFFERENT TEMPERATURES

		Patients														
	Time intervals	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Incubator 38° C.	Initial	25	20	21	19	23	20	25	16	18	17	21	23	19	17	22
	1 hr.	36	23	30	33	35	28	34	23	31	22	29	28	23	26	28
	2 hrs.	39	26	40	37	44	30	42	24	39	24	32	30	29	31	31
	3 hrs.	45	26	52	42	48	32	47	26	42	28	35	34	37	35	35
	4 hrs.	51	26	49	44	44	32	49	29	44	31	38	37	43	38	37
Room temperature 23° C.	Initial	25	20	21	19	23	20	25	16	18	17	21	23	19	17	22
	1 hr.	27	19	24	25	26	22	29	17	21	18	23	23	18	18	22
	2 hrs.	27	21	25	30	32	23	31	19	25	19	25	23	20	21	23
	3 hrs.	32	23	27	29	32	24	33	20	30	21	27	25	23	22	25
	4 hrs.	36	25	31	34	34	22	34	23	33	24	31	31	26	25	25
Refrigerator 5° C.	Initial	25	20	21	19	23	20	25	16	18	17	21	23	19	17	22
	1 hr.	28	21	27	26	25	23	29	17	21	18	23	23	19	19	20
	2 hrs.	28	26	21	24	24	20	28	18	25	19	23	25	21	19	21
	3 hrs.	32	20	25	26	29	22	29	19	27	21	24	24	22	19	23
	4 hrs.	27	20	27	25	25	24	31	20	29	23	26	24	22	21	26

In order to conserve space, all tenths of seconds were omitted from the above observations.

* Supplied as 'Stypven' Russell Viper Venom by Burroughs Wellcome & Co., Inc., New York, N. Y.

Graphic examination of the data of Table 1 indicated that for each temperature level, the prothrombin clotting time varied directly with the duration of storage. The rate of increase was greatest when the plasma was stored at 38° C. and least when the plasma was kept in the refrigerator. These points were investigated further by applying standard statistical procedures such as described in Snedecor's text.⁴

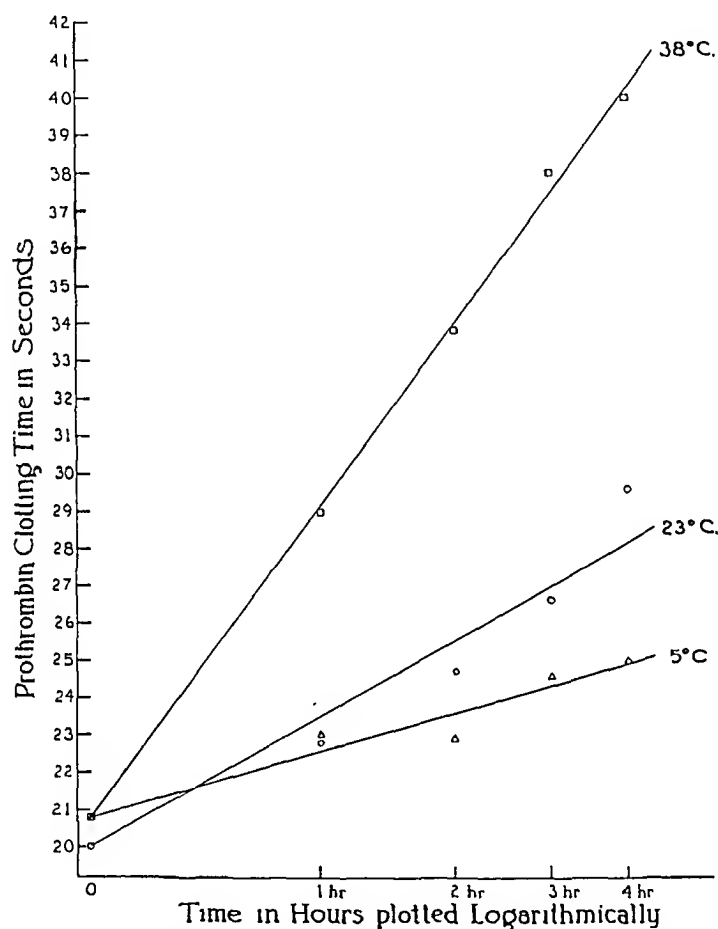


FIG. 1.—Graph showing increases in prothrombin clotting time as affected by temperature and duration of storage of plasma.

Statistical Analysis. At a given temperature the prothrombin clotting time apparently increases as a straight line function of the log of the storage time. This was tested for by performing an analysis of variance and calculating the variance ratio F in order to determine if the departures of the data from linearity were significant when compared with the variations within groups.⁴ F was found to be 0.046 for the incubator data, 3.452 for the room temperature data and 0.350 for the refrigerator data. As the tabular value of F for the 5% point was 3.98, it may be concluded that for none of the 3 curves was the departure from linearity sig-

nificant. A remarkably good fit was obtained with the incubator data and the poorest agreement between the observed values and the calculated line was obtained with the room temperature data. As Figure 1 shows, this was largely due to the high figures obtained for the 4-hour period.

It is not accidental that the sets of data for the 3 different temperatures determine 3 different lines since the slopes of these lines were found to differ significantly from each other. In testing this point, the standard error of the difference between two slopes was taken to be equal to the square root of the sum of the two variances of the slopes involved.¹ Values of the statistic t were calculated for the difference between the slopes of the room temperature curve and the incubator curve and for the difference between the slopes of the room temperature curve and the refrigerator temperature curve. The t values were found to be 4.726 for the former and 2.495 for the latter. Since both of these exceed the tabular figure of 1.960 for $P = 0.05$, both are to be regarded as significant. It may therefore be concluded that the prothrombin clotting time is a function of the temperature of storage as well as of the duration of storage.

Discussion. The results of this study reveal the necessity of completing the prothrombin clotting time test as soon as possible after the blood is obtained. In answer to the question of how much the prothrombin may increase on standing, the table of expected increases in clotting times was calculated from the equations of the 3 curves (see Table 2). The values of Table 2 are, of course, the expected values and individual samples may give increases which are greater or less than the tabular value. It will be observed that the expected increase is by no means negligible even for periods as short as 1 hour and that increased temperature greatly accelerates the increase in clotting time.

TABLE 2.—INCREASE IN PROTHROMBIN CLOTTING TIMES IN SECONDS⁴ OVER THE INITIAL VALUES AFTER STORAGE FOR GIVEN PERIODS OF TIME AT DIFFERENT TEMPERATURES

Length of storage period (in hours)	Refrigerator temperature 5° C.	Room temperature 23° C.	Incubator temperature 38° C.
1	1 8 sec.	3 6 sec.	8 4 sec.
2	2 8 "	5 6 "	13 3 "
3	3 5 "	7 1 "	16 8 "
4	4 1 "	8 3 "	19 5 "

The average initial prothrombin clotting time was 20.8 seconds. The above figures represent the expected increase over the initial value.

The theoretical implications of the results obtained are not obvious. However, there seems to exist some mechanism in the plasma, or operating on the plasma, by which the prothrombin clotting time is increased. This increase is proportional to the storage time, and the rate of increase is accelerated by an increase in temperature. It is reasonably certain, therefore, that prothrombin

is a labile substance. However, it is not clear whether the lability is due to deterioration of the prothrombin itself, to an enzymatic destruction of prothrombin, to the effect of an anti-thrombin or to some other cause. Further study is needed on these points.

Summary. 1. Prothrombin clotting times should be determined as soon as possible after blood is obtained.

2. In this study the prothrombin clotting time increased proportionally with the time of storage. At a given temperature, it increases as a straight line function of the log of the storage time.

3. The rate of increase of prothrombin clotting time is directly proportional to the storage temperature.

We wish to express our appreciation for the assistance and coöperation of Dr. Louis Bauman in whose laboratory this work was carried out, and also we wish to thank Miss Mary Hamlin for technical assistance.

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BOOK REVIEWS AND NOTICES

TEXTBOOK OF EMBRYOLOGY. By HARVEY E. JORDAN, M.A., Ph.D., Sc.D., Professor of Anatomy and Director of the Anatomical Laboratories, University of Virginia, and JAMES E. KINDRED, M.A., Ph.D., Professor of Anatomy, University of Virginia. Pp. 613; 470 figures and 31 plates. Fourth Edition. New York: Appleton-Century Company, 1942. Price, \$6.75.

THIS standard textbook has been thoroughly revised by its authors. The straightforward account of human development for which the work has always been distinguished has been elaborated to include recent experimental and comparative embryologic data. Many new figures have been added. Some figures leave something to be desired in the matter of craftsmanship in drawing, but their accuracy is not thereby impaired. It is one of the most useful books available for student or practitioner. R. W.

THE ELECTROCARDIOGRAM AND X-RAY CONFIGURATION OF THE HEART. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P., Cardiologist to the Mt. Sinai Hospital, New York, Assistant Professor of Clinical Medicine, Columbia University, New York. Pp. 404; 108 figures, 163 illustrations. Philadelphia: Lea & Febiger, 1942. Price, \$7.50.

INSTEAD of presenting systematically the various electrocardiographic and roentgenologic variations and abnormalities and then attempting to show what these abnormal findings suggest, the author of this book begins with variations and abnormalities in cardiac structure and position and then discusses the resulting effects on the electrocardiogram and roentgenogram. This somewhat novel method of presentation, together with the fact that the conclusions are often original and obviously based upon the author's wide experience and observation, results in a book that is fresh and interesting.

For similar reasons, the book naturally contains some conclusions that all students of this subject will not be willing to accept at the present time. It is doubtful, for example, if everyone will accept the conclusion that T wave inversion in hypertension is due to myocardial hypertrophy rather than to "left ventricular strain" or to myocardial disease. Likewise it is doubtful if every one will care to go as far as the author goes in using electrocardiograms and roentgenograms to diagnose individual chamber enlargement and even valve lesions. These facts do not detract from the value of the work. This particular reviewer found the book challenging and important. T. M.

TEXTBOOK OF PATHOLOGY. By SIR ROBERT MUIR, M.A., M.D., Sc.D., LL.D., F.R.S., Emeritus Professor of Pathology, University of Glasgow, Honorary Pathologist to the Western Infirmary, Glasgow. Fifth Edition. Pp. 991; 599 figures. Baltimore: Williams & Wilkins Company, 1941. Price, \$10.00.

THIS edition includes the important additions and modifications in the field of pathology in the past 5 years, necessitating an increase of 119 pages since the second edition. The aim continues to be borne in mind that a book was written primarily for students and that an understanding of principles is of more importance than a knowledge of the rarer abnormalities.

The professional pathologist, therefore, should not expect to find the considerable, though still inadequate, detail that is to be found in the best American textbooks on the subject. As these also serve as a reference book for the graduate student, the Reviewer has long felt that the textbook-reference-book dilemma could best be "straddled" in a single volume, by including a maximum amount of detail consonant with readability, but picking the less important matter out in small type. Aside from this aspect, we recognize Muir's textbook as a sound, reliable presentation, the English terminology and slight differences in concept not constituting a major obstacle.

E. K.

HÉRÉDITÉ MENDELÉENNE ET ANALYSE COMBINATOIRE. By Dr. E. -L. ROULET. Pp. 189. Genève: Georg et cie, 1941. Price, 12 Swiss francs.

This is a brief mathematical treatment of multiple factor inheritance, which contains very little that is new. The short bibliography lists no publication of H. S. Jennings, who covered much the same ground nearly 30 years ago, nor does the author seem to be aware of the work of the three leading mathematical geneticists of today, Sewell Wright, J. B. S. Haldane and R. A. Fisher. This book appears to emphasize the fact that the transference of the knowledge of genetics across national borders is not as good as it should be.

C. Z.

THE ESSENTIALS OF OCCUPATIONAL DISEASES. By JEWETT V. REED, B.S., M.D., F.A.C.S., and A. K. HARCOURT, B.S., M.D., Indianapolis, Ind. Pp. 225. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.50.

In our industrial expansion the protection of workers against occupational diseases and accidents has assumed increased importance and is demanding the close attention of the entire medical profession. With the exception of doctors already in service it must be assumed that every practising physician is likely to be called upon for service in this field and at almost any time. This volume will be useful to all physicians and to engineers and others concerned with safety work, and with the prevention of accidents. The authors have had 30 years' experience practising industrial medicine and surgery, and their volume provides answers to the great majority of questions that are likely to come up if, indeed, it may not be found complete in this regard.

The first chapter deals extensively with chemical poisons, the second with physical agents which may become industrial hazards; subsequent chapters discuss industrial dermatoses, occupational diseases of the lungs, malignant diseases associated with occupation, diseases due to infections, and functional disturbances associated with occupation.

There is an extensive bibliography. Especially valuable is a large folded table of potential industrial health hazards. This table is arranged with a classification of 108 industries in column form at the left, while across the top, at the heads of successive columns, are 79 recognized hazards. Thus it is possible, at a glance, by following the spaces across to identify the hazards which are most likely to be met in the industries enumerated. Industrial Medicine is essentially preventive medicine. When an accident occurs, or when an employee begins to show signs of intoxication resulting from the inhalation of a volatile poison, the physician has failed in his duty. As time goes on this point of view will be more and more emphasized. It is, therefore, necessary for the industrial physician to understand hazards so well that the employees under his care will never be exposed to serious risk. The volume is well printed and attractively bound. At times the diction becomes colloquial, but the documentation is excellent. The index is very full.

A. H.

THE MEDICAL APPLICATION OF THE SHORT WAVE CURRENT. By WILLIAM BIERMAN, M.D., Attending Physical Therapist, Mount Sinai Hospital, New York City; Assistant Clinical Professor of Therapeutics, New York University College of Medicine. With a chapter on Physical and Technical Aspects by MYRON M. SCHWARZSCHILD, M.A., Physicist, Beth Israel Hospital, New York City; Instructor of Physics in Radiology, New York University College of Medicine. Second Edition. Pp. 344; 87 illustrations. Baltimore: William Wood (Williams & Wilkins Company), 1942. Price, \$5.00.

THE mode of action and the therapeutic effects of short wave therapy is a much debated subject. Some investigators, chiefly American, maintain that the therapeutic effects are derived solely from the heat generated by the current; while others, mostly Europeans, believe that the effect is due to a specific action which may be either independent of or superimposed on the thermic effect. The author of this book belongs to the first of these groups. He does, however, reserve to himself "the privilege of retaining an open mind with regard to the possibility of the so-called 'specificity.'"

As in the first edition, the author has given a clear, scholarly exposition of the various phases pertaining to the subject of short wave therapy. Critically analyzing his own wide experience, he has also drawn abundantly from the experiences of others, even when their views do not agree with his. Among the numerous references in the book, there is a large percentage given to sources written in the principal foreign languages "in an effort to give the reader a comprehensive view of the material without requiring him to expend the labor necessary for the perusal of the voluminous and polylingual literature now available."

The present edition has been thoroughly revised, much new material added and the subject matter brought up-to-date. The text begins with a brief history of short wave current, then follow chapters on the physics of short wave current, temperature determinations in the human, physiologic responses to local heat and local short wave current, specificity and technique. Next there follows a newly written chapter on fever therapy and finally one dealing with clinical applications—this latter chapter occupying approximately one-half of the volume. Numerous new well-drawn illustrations enhance the value of this edition. The text is clear, to the point and highly instructive. As a reliable guide not only for workers in short wave therapy but also for other medical practitioners and, last but not least, as an inspiration to further study, this is a valuable book. J. N.

A SHORT HISTORY OF CARDIOLOGY. By JAMES B. HERRICK, M.D., Emeritus Professor of Medicine, Rush Medical College; Consulting Physician to Presbyterian Hospital, Chicago. Pp. 240; 48 plates. Springfield, Ill.: Charles C Thomas, 1942. Price, \$3.50.

SELDOM are we privileged to have a thoughtful and entertaining, historical survey of a medical subject such as this is, written by one who himself has contributed notably to that subject. When this rare bird does occur, it needs no commendation from a reviewer, nor does Dr. Herrick's book. However, we would like to remark that the same observing, keen and studious mind and critical judgment that detected new clinical entities and differential diagnostic pictures has now been applied equally well in the search for a selection of those students of cardiology "who, because of their personality, their important writings, or their influence in the development of knowledge may properly be regarded as worthy of remembrance." Dr. Herrick emphasizes that his is a *Short* history, without intention of being encyclopedic, so that he has felt free to dwell heavily on biography and to omit some features, especially if non-clinical, that one will mi-

Also the limitation to three centuries, "say from Harvey (1628) to Roentgen (1896)," excludes many whom we should have liked to have read about in Dr. Herrick's charming style. Aristotle, Herophilus and Erasistratus, Galen, and Vesalius and others are fortunately not left out entirely; but one would have liked to have read of Realdus Columbus, Sarpi, Carl Ludwig, Kölliker, Waller, the "congenital cardiologist" (including Maud Abbott), Broadbent, Richard Cabot, Libman, the heart surgeons, and by no means least, the author himself. We may hope that with the many useful days that are ahead of him, he may see fit to eliminate "Short" from the title and expand his history in both chronologic directions.

Even in these wartime days, I would like to conclude with a relevant quotation from the author's Preface: "The history of medicine as a suitable subject for study can be warmly endorsed. It leads to a better understanding of the present status of medical knowledge, making clearer what is definitely established and what is still in the stage of theory or uncompleted experiment. It teaches the student the importance of going for information to monographs and original articles. It may lead him, if not in his undergraduate days, at least early in his practice, to read medical biography. Once acquired, this habit is more than an ephemeral pastime. As an avocation, the study of medical history, especially medical biography, with the collecting of medical books and prints, has many attractions. If not gone into with a too lavish expenditure of time and money and if not deferred too long, it may prove to be one of the delights of old age."

E. K.

BIOLOGICAL SYMPOSIA. . Volume VII, "Visual Mechanisms." Edited by HEINRICH KLÜVER, Professor of Experimental Psychology, the University of Chicago, and Member of the Otho S. Sprague Memorial Institute. Pp. 322. Lancaster, Pa.: The Jaques Cattell Press, 1942. Price, \$3.25.

THE publications of Biological Symposia represent valuable contributions to scientific literature; and this volume, dealing with Visual Mechanisms, is no exception. The topics in this volume were presented as a symposium at the Fiftieth Anniversary of the University of Chicago in 1941. The problems of vision were discussed from the physical, biochemical, physiologic, anatomic, histologic and psychologic points of view by Drs. Hecht of Columbia University, Krause, Polyak, Case and Klüver of the University of Chicago, Wald and Lashley of Harvard, Gellhorn and Bonin of the University of Illinois, Bartley of Washington University, Marshall and Talbot of Johns Hopkins, and Walls of Wayne University. The book is highly recommended to all physiologists (in addition to those concerned chiefly with visual problems) and to those ophthalmologists who desire a more complete understanding of that tremendously complex organ, the eye, and its connections with the central nervous system. The volume is well printed and richly illustrated.

J. C.

MYSELF, MY THINKING, MY THOUGHTS. By K. W. MONSARRT. Pp. 140; 24 figures. London: Hodder & Stoughton. University Press of Liverpool, 1942. Price, 7/6, net.

PRESENTING his treatise in an autobiographic form, this philosophic psychologist begins with a discussion of the "habit that human beings call 'thinking,'" and continues in Part I, "My Thinking," under the following chapter headings: My Self's Affirmations and Ideas, About Myself's Idea-Forming, My Remembering and Reasoning Self, Images, and The Matter-Mind or Energy-Mind Problem. This classification of what the writer

says about his own thinking comprises two main groups of thoughts: those which convey his self's assertions, and ideas which are described as ideas of relation.

Part II, "My Thoughts," where a selection is made from among his own thoughts under the following headings: Image of the Self as a System of Factors and the Image of the World, Interpreting and Explaining Images, Association and Balance, The Human Assembly, and Prospects. These various topics concern the writer's relations between his own powers and other powers. One chapter gives significance to the expression, "explaining images." Another discusses "what I name human needs, from my knowledge of my own states. . . ."

The final chapter considers the prospect of human well-being in the light of present-day trends of conduct, and the writer contends that criticism of human habits and thought is required, including inquiry into human thinking itself. In this erudite contribution, the author has attempted courageously the further elucidation of the complex subject, human thought.

N. Y.

ROENTGEN TREATMENT OF DISEASES OF THE NERVOUS SYSTEM. By CORNELIUS G. DYKE, M.D., F.A.C.P., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University; Director, Department of Radiology, Neurological Institute of New York; and LEO M. DAVIDOFF, M.D., F.A.C.S., Chief, Department of Surgery, Attending Neurological Surgeon, Jewish Hospital of Brooklyn. Pp. 198; 12 engravings, 7 charts, 16 graphs. Philadelphia: Lea & Febiger, 1942. Price, \$3.25.

THIS monograph is one of that small group of books which gives more than it promises. The authors state in their preface that a "compilation of our present knowledge is timely." A critical survey of the literature alone by such competent experts in their fields would have been a great contribution in view of the confusion that new apparatus and techniques have created in judging the results of Roentgen ray treatment. In reality, literature abstracts fill only a fraction of the book, and the results of personal experience of the authors over a period of 12 years prevail. Almost 200 carefully selected cases form the body of the book; of which over 80 are described in detail in their surgical and Roentgen ray treatments, their clinical course and final outcome. The combination of a neurosurgeon and a roentgenologist in the authorship of the monograph prevents any over-optimism concerning the curative effect of Roentgen ray therapy in the treatment and cure of brain tumors and other nervous diseases. Therefore, their true positive results deserve higher evaluation and should encourage appropriate application. This well-written booklet will serve as a useful guide for neurologists, neurosurgeons and roentgenologists alike "through the maze of facts and suppositions that have accumulated in this field."

F. L.

NEW BOOKS

The Hemorrhagic Diseases and the Physiology of Hemostasis. By ARMAND J. QUICK, PH.D., M.D., Associate Professor of Pharmacology, Marquette University School of Medicine, Milwaukee, Wis. Pp. 340; 9 tables, 23 figures, 1 color plate. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

Civilian Health in Wartime. By FRANCIS R. DIEUAIDE, M.D., Associate Professor of Medicine, Harvard Medical School, Mass. General Hospital. Pp. 328; several tables. Cambridge, Mass.: Harvard University Press, 1942. Price, \$2.50.

Biological Symposia. Vol. IX, *Sex Hormones*. Edited by F. V. KOCH, Frank P. Hixon Distinguished Service Professor of Physiological Chemistry and Chairman of the Department of Biochemistry of the University of Chicago, and PHILIP E. SMITH, Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 145; many figures and tables. Lancaster, Pa.: The Jaques Cattell Press, 1942. Price, \$2.50.

Annual Review of Biochemistry. Vol. XI, 1942. Editor, JAMES MURRAY LUCK, Stanford, Univ., and JAMES H. C. SMITH, Associate Editor—Carnegie Institution of Washington, Division of Plant Biology, Stanford Univ., Calif. Pp. 736. Stanford University P. O., Calif.: Annual Reviews, Inc., 1942. Price, \$5.00.

Annual Review of Biochemistry. Cumulative Author and Subject Index, Vols. I to X. Author Index compiled by LUCILE BROWNE, CHARLOTTE W. GIBB, FLORA L. HEWLETT, BETTY P. JUDSON, MARIAN PETERS and NANCY S. SMITH. Subject Index compiled by JANET I. LUCK. Pp. 344. Stanford University P. O., Calif.: Annual Reviews, Inc., 1942. Price, \$3.50.

Both an author and subject index are included. The subject index has been done in considerable detail and greatly adds to the value of these volumes as works of reference.

J. J.

Laboratory Directions in Biochemistry. By VICTOR C. MYERS, M.D., PH.D., D.Sc., Professor of Biochemistry, Western Reserve University. Pp. 288; 15 figures, many tables. St. Louis: C. V. Mosby Company, 1942. Price, \$3.50.

This manual is divided into 4 parts. Part 1 covers the usual qualitative experiments given in courses in Biochemistry to medical students. Quantitative work on urine is also given in this section. Part 2 is devoted to clinical chemistry and includes most of the usual quantitative determinations done in a hospital laboratory on gastric and duodenal contents, feces and blood. Part 3 is a special section covering the laboratory work for a course in biochemistry for dental students with references to many of the experiments in the first two sections. Part 4 is an appendix with notes on the use of colorimeters, analytical balance, etc.

Brief outlines of the courses given to the medical and dental students at Western Reserve University are also included.

J. J.

Ovarian Tumors. By SAMUEL H. GEIST, M.D., Attending Gynecologist, Mount Sinai Hospital; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University. Pp. 527; 312 illustrations. New York: Paul B. Hoeber, Inc., 1942. Price, \$10.50.

Manual of Standard Practice of Plastic and Maxillofacial Surgery. Military Surgical Manual I. Prepared and Edited by the Subcommittee on Plastic and Maxillofacial Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council, and Representatives of the Medical Department, U. S. Army. ROBERT H. IVY, Chairman. Pp. 432; 259 figures. Philadelphia: W. B. Saunders Company, 1942. Price, \$5.00.

Ophthalmology and Otolaryngology. Military Surgical Manuals II. Prepared and edited by the Subcommittees on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 331; 51 figures. Philadelphia: W. B. Saunders Company, 1942. Price, \$4.00.

Carcinoma and Other Malignant Lesions of the Stomach. By WALTMAN WALTERS, B.S., M.D., M.S., in Surgery, D.Sc., F.A.C.S., Surgeon, Mayo Clinic; HOWARD K. GRAY, B.S., M.D., M.S. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; JAMES T. PRIESTLEY, B.A., M.D., M.S. in Experimental Surgery, Ph.D. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; and Associates in the Mayo Clinic and Mayo Foundation, Rochester, Minn. Pp. 576; 143 illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, \$8.50.

- Abdominal and Genito-urinary Injuries.* Military Surgical Manual III. Prepared under the Auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 243; 28 figures. Philadelphia: W. B. Saunders Company, 1942. Price, \$3.00.
- Biochemistry and Morphogenesis.* By JOSEPH NEEDHAM, F.R.S., Sir William Dunn Reader in Biochemistry and Fellow of Gonville and Caius College, Cambridge. Pp. 785; 328 figures. Cambridge: The University Press—New York: The Macmillan Company, 1942. Price, \$12.50.
- The Food You Eat.* By SAMUEL and VIOLETTE GLASSTONE. Pp. 278; 18 plates. Norman, Okla.: The University of Oklahoma Press, Publishing Division of the University, 1942. Price, \$2.25.
- The Hospital Care of the Surgical Patient.* By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic, and FRANKLIN L. SHIVELY, JR., M.D., Assistant Surgeon, Cleveland Clinic. Pp. 184; 21 figures. Springfield, Ill.: Charles C Thomas, 1943. Price, \$2.50.

NEW EDITIONS

Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York and Bellevue Hospitals; and Associate Editor for *Diseases of the Nervous System*; and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College; Attending Physician, New York Hospital; Visiting Physician in Charge, Neurological Service, Bellevue Hospital; Consulting Physician, New York Neurological Institute. Fifth edition. Pp. 1744; 173 figures, some in color. Philadelphia: W. B. Saunders Company, 1942. Price, \$9.50.

This 1-volume text continues the general format used in previous editions, with the addition of a number of new contributors bringing the total to 144, most of whom are members of medical school faculties. The addition of a significant number of well-chosen illustrations is a departure from former editions. Certain changes in the arrangement, text, etc., are made in accordance with present-day knowledge, with significant references placed at the end of most subjects. The book continues to be easily readable, well arranged, and one of the best 1-volume textbooks on medicine. M. T.

The Microscope. By SIMON HENRY GAGE, Emeritus Professor of Histology and Embryology in Cornell University. Seventeenth Edition. Pp. 617; 313 figures. New York: Comstock Publishing Company, 1942. Price, \$4.00.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (Lond.), Professor of Pathology in the University of London; Pathologist to St. Bartholomew's Hospital, Formerly Examiner in Pathology in the University of London; and LAWRENCE P. GARROD, M.A., M.D., B.Ch. (Camb.), F.R.C.P. (Lond.), Professor of Bacteriology in the University of London, Bacteriologist to St. Bartholomew's Hospital, Formerly Examiner in Pathology in the University of Cambridge. Fourth Edition. Pp. 346; 35 illustrations. Philadelphia: The Blakiston Company, 1942. Price, \$5.50.

With the 4th edition coming 4 years since the last, the greater part of this book has been rewritten in accordance with newer knowledge. "Inflammation and related phenomena now occupy 2 introductory chapters instead of 1. The chapters on vitamin deficiency diseases and on essential hypertension, and the extensive sections on crush syndrome and extra-renal azotemia are entirely new." As was mentioned in their 1st edition, the authors have continued largely to confine the text material to those observations related to the commoner problems of disease. Although useful to pathologists, those medical workers not in this field will probably benefit most from this easily readable volume, which integrates the newer knowledge with older established material. M. T.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.*

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE,
DENVER, COLO.

AND

GEORGE S. JOHNSON, M.D.

PROFESSOR OF NEUROPSYCHIATRY, STANFORD UNIVERSITY SCHOOL OF MEDICINE,
SAN FRANCISCO, CALIF.

THE EXPERIMENTAL NEUROSIS IN ANIMAL AND MAN

THE lack of experimental method in psychiatry has been one of the reasons for the breach which tends to exist between it and other fields of medicine. The relative abstractness and complexity of causal factors in mental disorders made the experimental approach seem insurmountable until the discovery of the conditioned reflex and the first description of an "experimental neurosis" by the Russian physiologist, Pavlov. With this came the opportunity, still largely unexploited, to study in the laboratory the relative importance of various types of conflict situations, of genetics and of somatic factors in the production of symptoms. The analysis of these symptoms and the detection of means for their alleviation also became possible. Abnormal behavior has been synthesized in a variety of animals, including the dog, sheep, goat, rat, rabbit, cat, pig, pigeon, chimpanzee and ape. In a rudimentary way this synthesis has also been accomplished in man. Thus a foundation has been laid for the science of "comparative psychiatry."

Experimental Neuroses in Animals. *Definition: Comparison With Human Psychoneuroses.* The term "experimental neurosis," devised by Pavlov,²⁸ has been generally accepted to describe abnormal behavior of a more or less chronic nature which is produced experimentally. Cook^{7b} gives the following criteria: (1) the abnormal behavior must be maladaptive behavior; (2) it must further be behavior which involves a change in a given animal's responses; and (3) it must be behavior which persists at least as long as the animal is in periodic contact with the precipitating situation.

Most observers have carefully avoided identifying the "experimental neurosis" of animals with the human psychoneurosis. However, all point out similarities in the objective manifestations. Liddell²² states,

*Now on active service with the Armed Forces.

"If we begin matching animal and human situations we involve ourselves in insoluble problems. We therefore chose to attempt to standardize a neurosis-producing situation, and then to explore in detail the psychosomatic consequences of the condition. We have no desire to identify the experimental neurosis in sheep with any form of human mental disorder. However, its origin suggests similarity to the human situation, where difficulties arise under social pressure."

Mechanism of Production and Symptomatology. Pavlov's first neurotic dog had previously been trained to react to an electrical stimulus applied to a skin area by increased salivation (conditioned reflex), instead of the normal reaction of defense (unconditioned reflex). When the stimulus was applied to a variety of places on the skin instead of a specific area, a limit was finally reached. The conditioned reflex was lost, a violent reaction of defense appeared and the animal became restless and excited.

Probably the best known of Pavlov's experimental neuroses occurred in a dog which had learned to differentiate between a circle, associated with feeding (positive or excitatory stimulus), and an ellipse with a ratio of semi-axes 2:1, not associated with feeding (negative or inhibitory stimulus). Further differentiation was attempted by approximating the shape of the ellipse to that of the circle. All went well until an ellipse with ratio of semi-axes 9:8 appeared. "After 3 weeks of work upon this differentiation not only did the discrimination fail to improve, but it became considerably worse, and finally disappeared altogether. At the same time the whole behavior of the animal underwent an abrupt change. The hitherto quiet dog began to squeal in its stand, kept wriggling about, tore off with its teeth the apparatus for mechanical stimulation of the skin, and bit through the tubes connecting the animal's room with the observer, a behavior which had never happened before. On being taken into the experimental room the dog now barked violently, which was also contrary to its usual custom: in short it presented all the symptoms of a condition of acute neurosis."

Pavlov^{4,28} expressed the belief that the experimental neurosis was due to one of the following causes:

1. Excessive stimulation of the inhibitory processes. This occurred in the experiment just cited.

2. Conflict between cortical inhibitory and excitatory processes. This mechanism is described in a dog which was able to discriminate between a positive tactile stimulus at the rate of 24 per minute and a negative tactile stimulus at the rate of 12 per minute. When one type of stimulus followed the other without a pause, the animal developed signs of a neurosis which lasted 5½ weeks.

3. Extraordinarily strong or unusual stimuli. This is illustrated by the results of a flood which made it necessary for the animals to swim for their lives through a terrific storm. All of their conditioned reflexes disappeared, and one of them developed a chronic neurotic condition.

Investigation of experimentally produced neuroses have been continued in this country by a number of workers, including Gantt,¹⁶ Liddell and his associates,^{1,2,3,4,23} Dworkin,^{10,12} Maier,^{25,26} Cook⁷ and others.^{9,15,19,29}

Gantt¹⁶ has extended Pavlov's analysis to a study of systems other than the alimentary tract. This has included respiratory, circulatory,

urinary, sexual and muscular activity in addition to social relationships. He describes (1) abnormalities in the rhythm and type of respiration, (2) increase of the heart rate, (3) intractable pollakiuria (as frequent as 30 times per hour) and (4) abnormally frequent erections and premature ejaculations. The animals tend to improve temporarily after sexual relations or after being petted by a human companion. Gantt notes "a tendency toward disintegrative action as a psychobiological unit."^{16a}

The Cornell University group, led by H. S. Liddell, has succeeded in producing chronic neurotic states in a number of animals, notably the sheep, using conditioned reflex techniques. Anderson and Parmenter¹ describe three types of procedure that they have successfully employed: (1) difficult differentiations, (2) experimental extinctions and (3) rigid time schedules. The first procedure is similar to that used by Pavlov in the circle-ellipse differentiation. The second consists of following the positive (food) stimulus with an exceedingly long series of negative (no food) stimuli. The third involves the use of a monotonous routine of alternating positive and negative stimuli; *i. e.*, pure tone of 435 cycles; shock; 7 minute pause; pure tone of 900 cycles; no shock; 7 minute pause; pure tone of 435 cycles; shock; 7 minute pause; pure tone of 900 cycles; no shock; animal released. With this sequence the conditioned reflexes increase in strength. Finally the level of excitation is so greatly augmented that the animal responds with a positive reaction (reaction of defense) to both the positive and negative stimuli and, indeed, to accidental noises, finally developing the typical findings of an experimental neurosis. "His nervousness is the result of the certainty of being confronted with the necessity for making an adequate psychobiological adjustment, an adjustment which is impossible since he cannot escape from the experimental environment. It does not matter whether the stimulations which he is accurately anticipating are of an unpleasant or pleasant nature—shock or food."

Anderson and Parmenter give a detailed description of the manifestations of the experimental neuroses seen in their sheep and dogs, observed over periods as long as 12 years in a single animal:

1. *Hyperirritability, Overactivity to Stimulation and Restlessness During the Experiment.* Sensitivity to touch or unexpected noise appeared among the earliest symptoms. The animal responded by running away, trembling or urinating. During the period of stimulation the animal seemed ready to react before any cause appeared. Some exhibited violent motor reactions and vocalizations. Before each experiment and in the intervals between stimuli the animals were tense and extremely restless; a marked increase in the number of spontaneous movements were noted.

2. *Inhibitory Types of Reaction.* These were much less frequent than the excitatory variety. One dog, who had previously developed the hyperexcitable type of behavior noted above, later responded with little or no movement for long periods of time. The limbs appeared rigid and somewhat resistant to changes in position. They could, however, be placed in various abnormal positions. Anderson and Parmenter called this condition "pseudo-decerebrate rigidity." A psychiatrist might have called it catatonia with waxy flexibility. In 2 of the sheep a similar though more transient and localized inhibitory state

was observed. Instead of the normal response of flexion of the leg following the shock, the animal vigorously extended the leg. The pulse was found to be rapid and labile during the interval periods, just as in the excitatory neurosis, in spite of almost complete absence of muscular movement.

3. *Transfer of the Motor Reaction Pattern.* This occurred in several of the neurotic animals which had developed spontaneous movements of the stimulated leg in the intervals between stimuli. These spontaneous movements shifted to other muscle groups, such as the opposite leg or the head and neck. The authors suggest the similarity between this shift and the unaccountable transfer of pains in neurotic patients from one location to another.

4. *Diurnal Neuromuscular Activity.* The activity in a 24 hour day was measured by means of a pedometer attached to the foreleg. The total activity in the neurotic animal was not particularly different than that in the normal animal. The neurotic, however, showed about as much activity during the night as during the day, whereas the normal showed little or no activity during the night. The neurotic animal, like the neurotic human, apparently suffers from insomnia.

5. *Respiratory Manifestations.* "One of the most noticeable changes marking progress of the experimental neurosis in the sheep as seen in the laboratory is the increase in the average respiratory rate as well as changes of pattern and rhythm which accompany it." The animals were studied not only in the laboratory but also in the barn, using a "long distance" pneumograph. Frequent apneic pauses were sometimes followed by deep inhalations and exhalations.

6. *Cardiac Manifestations.* "Sheep in which an experimental neurosis has been developed reveal, upon examination, a cardiac disorder which is characterized by a rapid and irregular pulse and by extreme sensitivity of the heart's action to conditioned and other stimulation. Rapid increases of rate occur in response to mildly startling stimuli which have no effect upon the pulse of the normal sheep. Spontaneous variations of rate are observed both in the barn and in the laboratory. Conditioned stimulation produces a considerable and long-continued increase in pulse rate associated with premature beats and sometimes coupled rhythm."³

7. *Micturition and Defecation.* The neurotic sheep characteristically retained his urine and feces until the termination of the experiment. As soon as the experimenter began to release the animal, urination and defecation occurred. This did not happen in normal sheep. Neurotic dogs frequently urinated during episodes of excitability but did not defecate.

8. *Social and Emotional Manifestations.* Shyness was one of the most striking symptoms exhibited by both the neurotic dogs and neurotic sheep. They tended to remain alone, lacking the gregariousness seen in the normal. When it was necessary for them to get their food from a common source, they went hungry. The dogs did not join in the playful running and barking activities of their neighbors. When cornered, these shy neurotic animals became aggressive and would bite, struggle or kick. The sheep exhibited no change in their sexual reactions. One of the neurotic male dogs lacked interest when a bitch in heat was placed in the pen with him.

Liddell²² takes exception to Pavlov's hypothesis that the cause of the abnormal behavior is a clash between intense cortical excitations and inhibitions. He points out that animals allowed to run at will in a maze attempting to solve extremely difficult problems never develop disturbances. Some of these same animals soon become neurotic when confined in the laboratory. "We believe that the experimental neurosis is caused by the equivalent of a human conflict situation. The dog or sheep standing quietly in the harness has through habit relinquished its neuromuscular freedom. When such an animal is called upon to anticipate food or shock at certain intervals but not at others it cannot escape the issue. Its reaction, whether motor or secretory, represents a decision arrived at. When the task of making the necessary decision is beyond the individual's capacity, its nervous system undergoes a drastic change in its mode of functioning and the signs of experimental neurosis appear."

This concept has been tested in Liddell's laboratory by Sutherland and Curtis,⁸ using the pig. It has been verified by Dimmick, Ludlow and Whiteman⁹ in the cat and by Cook^{7b} and Witkin²⁹ in the rat. Dworkin has made another contribution, although his experiments involved different animal species. Harnessed dogs and free-moving cats were subjected to a situation involving delicate sound discrimination. Only the harnessed dogs developed severe neurotic disturbances, in spite of the cat's poorer ability in discrimination of sounds. Cook^{7b} attempted to produce abnormal behavior in the white rat by a variety of methods. He was successful with only one. In this method the rat was placed in a stand during the period of experimentation and all movement save struggling was impossible. The unsuccessful methods were essentially similar to the successful, involving opposing excitatory and inhibitory responses, save for the lack of restricted movement. Like Liddell he concludes, "If, in a stressful situation, activity other than that involved in the critical response is sufficiently limited an 'experimental neurosis' will result."

Maier,²⁵ on the other hand, describes the production of abnormal behavior in the rat under conditions of frustration. Unusual motor phenomena, especially seizures, appeared when the animals were confronted by food which is unattainable on one end and an objectionable stimulus, such as a blast of air, on the other. He expresses the belief that this frustration is a different type of situation than Pavlov's conflict between inhibitory and excitatory processes and Liddell's concept of the importance of restriction of neuromuscular freedom. His work has been challenged by Morgan²⁷ who notes that seizures did not appear in Maier's rats in the absence of an acoustic stimulus. Morgan was able to produce seizures as frequently with auditory stimuli alone as with auditory stimuli combined with "conflict." He therefore concludes that the seizures are purely audiogenic in nature.

Karn¹⁹ has noted abnormal behavior in an unrestrained cat attempting to solve a problem in a double alternation temporal maze.

Susceptibility to Experimental Neuroses (Rôle of "Constitution"). Almost all investigators have agreed that the development of a chronic behavior disturbance is limited to a fraction of all animals tested. Pavlov related this susceptibility to the basic "temperament" of the animal. He noted the appearance of neurotic behavior only in dogs

which were of the "melancholic" type (timid and docile with predominance of inhibitory processes) or of the "choleric" type (excitable and aggressive with predominance of excitatory processes). Initially well-balanced animals ("phlegmatic" or "sanguine" types) never developed chronic disturbances in behavior.

Of 3 dogs that Gantt subjected to identical conflict situations,¹² only 1 developed a "chronic and apparently incurable neurosis." Anderson and Parmenter stated that but 7 out of 28 sheep and 3 of 26 dogs which they studied developed experimental neuroses. Furthermore the time of development varied from as little as 10 days to as long as 7 years from the beginning of an experiment. Cook stated that his rats possessed varying degrees of constitutional predisposition. Three of 6 animals used in one experiment developed chronic symptoms of abnormal behavior.

As yet, no controlled study of the relationship of heredity to susceptibility to the experimental neurosis is available.

Somatic Factors. Gonads: Pavlov and Petrova⁴ studied the activity of dogs before and after castration. After castration the conditioned reflexes were chaotic. Abnormal behavior occurred not only in the "melancholic" and "choleric" types of animals but also in previously well-balanced animals. It tended to be transient in the latter. "Numerous experiments have shown that the main feature of the nervous activity of castrates is mostly a greatly weakened inhibitory process." Thyroid: Thyroidectomy appears to effect the behavior of the dog more than that of the sheep.¹ Profound weakness or disappearance of the conditioned motor and salivary reflexes was observed in thyroidectomized dogs. It is noteworthy that administration of 1 gm. of thyroid extract daily to neurotic sheep did not aggravate the condition. Adrenals: The possible rôle of the adrenals has been suggested by the report of Liddell and his coworkers²³ on the effects of administration of extracts of adrenal cortex to neurotic sheep. Nervous symptoms were improved and the vigor of the conditioned reflex was increased. Adrenalin, on the other hand, increased the behavior disturbances and decreased the vigor of the conditioned reflex. Cerebral cortex: Jacobsen, Wolfe and Jackson¹⁸ produced a neurotic disturbance in a chimpanzee in the course of experiments testing recent memory. After extirpation of both frontal lobes the animal became more friendly and had no further temper tantrums in spite of a great increase in the number of errors made during the testing procedure.

Treatment. The therapeutic armamentarium has consisted of (1) rest, (2) sedatives, (3) eliminating the "conflict" and (4) hormones.

Rest has seldom succeeded in producing permanent alleviation of symptoms. Pavlov noted that 1 animal, after being alone "for a very long time," spontaneously recovered. Anderson and Parmenter observed a spontaneous remission in a senile sheep who had tenaciously clung to his neurosis for 9 years, although the animal had previously been exposed to long periods of rest and other attempts at therapy. They gave 1 animal a "rest cure" for 3 years, only to have the neurosis reappear after 5 days of experimentation. In 1 of Gantt's dogs, a rest of 18 months in the laboratory was not followed by improvement. A 2-months' vacation on a farm resulted in marked improvement until the animal returned to the laboratory, when the symptoms returned in

several weeks. After another 18-months' rest in the country, the neurotic symptoms reappeared, though less severe, in the laboratory.

Pavlov believed that the most effective therapeutic agent for his dogs to be the administration of bromides over a period of about 10 days. The temporary use of this drug resulted in permanent improvement in excitable, neurotic dogs. He believed that bromides do not act by diminishing the excitability of the nervous system, inasmuch as positive conditioned reflexes remained constant after its use, but that it strengthens the intensity of internal inhibition. Dworkin, Raginsky and Bourne¹¹ verified the persistent effect of this drug. Neurotic symptoms, they found, were quickly abolished by sodium amytal, nembutal, alcohol and avertin, but these symptoms returned within 24 hours. Anderson and Parmenter agreed that single doses of sodium amytal and alcohol have only transient effect; the same applied, however, to a single dose of sodium bromide. Continued administration of small doses of phenobarbital to a neurotic sheep resulted in definite decrease in "nervousness" and increase in coöperation. This improvement was maintained after cessation of the drug, although the authors felt that this may have been on the basis of a spontaneous remission.

A type of desensitization has been successfully utilized by Anderson and Parmenter. One of their dogs developed the typical symptoms of an experimental neurosis after being completely unable to make a successful differentiation between the metronome beating at the rate of 120 per minute (followed by a shock) and the metronome beating at the rate of 36 per minute (not followed by shock). When the sound of a buzzer was added to the negative stimulus, the animal succeeded in making the differentiation. It then became practically normal and continued so during the remaining year of the experiment.

Improvement following the use of extract of adrenal cortex has already been noted.

Experimental Neuroses in the Human. Experimental production of abnormal behavior in the human, partly of necessity, has been somewhat limited. A start in this direction, however, has been made by (1) the conditioned reflex technique employed by Krasnogorski,²⁰ (2) the creation of complexes in the hypnotic state as suggested by Luria²⁴ and (3) the techniques of topologic and vector psychology described by Lewin and his colleagues.^{5,6,21}

Conditioned Reflexes in Children. Krasnogorski has used the classical conditioned reflex techniques of Pavlov. Behavior disturbances were produced by difficult differentiations and delayed reactions. Under these experimental conditions the children reacted much the same as Pavlov's dogs. Loss of the conditioned reflex, restlessness, irritability, asocial behavior and refusal to return to the laboratory were among the symptoms noted.

The Luria Technique. Artificial emotional complexes are created while the subject is under deep hypnosis. For example, the hypnotized subject is given the following instructions: "When you come into the experimental room and sit before the apparatus, you will want to repeat two words—red and blue, red and blue. However, you will not be able to speak them, although they will continue to be present in your thoughts." Thus two obligatory but opposing tendencies are created. In the post-hypnotic period the subject, having an amnesia for the

suggested complex, is asked to associate freely, to repeat the names of various colors including the disturbing ones or to define the color of objects such as blood. When he finds himself unable to carry out these simple requests—without conscious reason—he becomes perplexed and upset. An acute disorganization of behavior may be induced as shown by the disturbance in the character of the associative processes and by increased tension and tremor which is recorded on a kymographic tracing.

This method has been utilized by Huston, Shakow and Erickson,¹⁷ Erickson¹⁴ and Eisenbud.¹³ The latter produced symptoms in a susceptible subject by suggesting hostile, aggressive impulses during the hypnotic period.^{13a} Although the subject was not consciously aware of these impulses in the awakened state, he complained of headache and irritability. Using a modification of the Luria technique, Eisenbud tested the hypothesis that the excitement of the parasympathetic division of the autonomic nervous system varies with the function of repression.^{13b} This was done by substituting measurements of parotid gland secretion and of gastric motility for the association procedure used by Luria.

Topologic and Vector Psychology. This is essentially a mathematical approach employing psychobiologic data. The topologic situation consists of the individual in his own *life space*. The individual's personality structure may be differentiated into his *inner personal regions*, consisting of needs, goals, aversions and so forth, and a surrounding *motor perceptual region*, by which the inner personal regions make contact with the outer world. The needs, goals and aversions of the individual give rise to tension systems, which induce in turn corresponding environmental regions to acquire positive or negative valences. The interaction between tension systems and valences results in a force acting on the individual, drawing him toward regions of positive valence and repelling him from regions of negative valence. The magnitude and direction of the forces may be ascertained; hence they are defined as *vectors*. When the individual is suspended between opposing vectors of the same magnitude, a *conflict situation* results. The concept may be illustrated as follows:

A child desires a piece of candy. The child's mother will punish him if he takes it. The child's desire, representing an inner personal region, causes the candy to assume a positive valence. The fear of punishment assumes a negative valence, hence represents an opposing vector. Thus, a conflict situation is established.

Dembq⁵ and Brown,⁶ using this concept, have established experimental methods which subject the individual to severe frustration and subsequent disorganization of the personality. The subject is requested to solve a problem for which no solution exists. Not being aware of this, emotional tensions arise which may result in regressive types of behavior.

Conclusion. The experimental method opens a valuable testing ground for the hypotheses of psychopathology and for the concepts of psychosomatic medicine. It should not be expected to supplant the historical, analytical approach of psychiatry, but rather to be a useful adjunct to it.

ALBERT J. LUBIN, M.D.

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SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.

HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

AND

C. G. JOHNSTON, M.S., M.D.

PROFESSOR OF SURGERY, WAYNE UNIVERSITY, DETROIT, MICH.

THE ETIOLOGY AND PATHOGENESIS OF ACUTE
HEMORRHAGIC PANCREATITIS*

I. Introduction. Acute pancreatitis, as it occurs in man, seems to be manifest in two different forms which present a similar clinical picture at their onset, but which follow strikingly different clinical courses and have vastly different prognoses. Both forms are characterized by the sudden dramatic onset of constant, agonizing, epigastric pain, accompanied by marked prostration. There are usually epigastric tenderness and rigidity, nausea and vomiting, and moderate fever and leukocytosis. Various other signs and symptoms may be present, but in general the picture is one of an acute abdominal catastrophe,

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occurring in the upper half of the abdomen, which is not specific for either form, and not very different clinically from other conditions such as a perforated peptic ulcer, acute cholecystitis, and intestinal obstruction.

In a few hours to a few days, the picture presented by the two forms starts to diverge markedly.

In one form the disease follows a fulminant course characterized by shock and the picture of a profound toxemia, and terminates fatally, in the majority of cases, in a few days to a few weeks. In the other form, the disease seems to be at or very near its peak almost at the time of onset. This picture persists for from several hours to a few days and then subsides, usually without residual symptoms. The pancreas in the fulminant form is the seat of varying degrees of hemorrhage, necrosis and/or suppuration; in the benign form there is only marked edema of the pancreatic and peripancreatic tissues. The varied pathologic lesions seen in the fulminant form have been considered by some authors to be states of one pathologic process and they have called the disease "Hemorrhagic Necrosis of the Pancreas,"⁵⁷ "Hemorrhagic Pancreatic Necrosis,"^{735,35a} "Acute Pancreatic Necrosis,"^{24,75} and "Acute Hemorrhagic Pancreatitis";^{13,54,62,67a,76} others^{24,25,44} have classified it into three groups depending upon which pathologic lesion was dominant. This form seems to be a clinical entity regardless of the specific lesions; for it I shall use the term acute hemorrhagic pancreatitis in this sense throughout this paper. The mild form has been called "subacute pancreatitis,"⁶⁹ "acute interstitial pancreatitis,"^{29,38} or "acute edematous pancreatitis";^{16,17,29,69}

Fitz,³⁴ in 1888, gave the first accurate description of acute hemorrhagic pancreatitis, and since that time this form of the disease has held a fairly prominent place in medical literature. Archibald¹ in 1913 called attention to edema of the pancreas as a result of experimental study of hemorrhagic pancreatitis in animals, and in 1924 Zoepffel⁶³ differentiated 4 cases of acute edema of the pancreas seen at operation from 7 cases characterized by hemorrhage and necrosis of the pancreas. In 1933 Elman²⁹ collected 33 cases from the literature and presented them, together with 4 of his own cases, "to establish as a clinical and pathologic entity, the undoubted occurrence of a special type of acute pancreatic disease, tentatively designated as acute interstitial pancreatitis, which is characterized by the presence of edema, swelling and induration of the pancreas without necrosis, hemorrhage, or suppuration." Since that time this form of the disease has been fairly widely recognized by the medical profession.

The term "acute pancreatitis" as used in the literature from 1880 until 1933 refers only to the fulminant form of the disease. During this time acute pancreatitis was considered a rare disease with an extremely high mortality. Despite its infrequent occurrence it was the subject of a considerable amount of investigation, and its etiology and pathogenesis were the source of much study and controversy. Because of this fact most of the information relative to the etiology and pathogenesis of acute pancreatitis pertains to the fulminant form of the disease only, and experimental work has been largely directed toward the production and study of hemorrhagic pancreatitis.

It is important to remember that when much of this work was done,

the edematous form of the disease was not recognized and that this may have been the source of confusion in some instances. Careful scrutiny of clinical studies of acute pancreatitis strongly suggests that this factor has been responsible for some of the discrepancies that exist in the literature, especially in regard to case-fatality statistics. Its influence upon experimental studies also probably has been important.

The relationship between these two forms of acute pancreatitis is unknown at the present time and accurate classification awaits further knowledge of their etiology and pathogenesis. With this in mind as a future objective, it is the purpose of this paper to review some of the clinical and experimental evidence bearing upon the etiology and pathogenesis of acute hemorrhagic pancreatitis.

II. Pathologic Anatomy of Hemorrhagic Pancreatitis.^{24,25,28,34,44,46,55,62,67a}

The pathologic changes seen in the pancreas in hemorrhagic pancreatitis are varied depending upon the degree of hemorrhage, necrosis, and/or suppuration present. In some cases hemorrhage into the pancreatic parenchyma may be massive, amounting to what has been called "pancreatic apoplexy," and no necrosis or suppuration may be seen. In other cases there may be massive necrosis of the gland with very little hemorrhage or suppuration. In still other cases, the gland may present only one or several areas of suppuration and occasionally the entire gland is involved, with formation of a large sequestrum. It is believed that these latter cases are true abscesses due to bacterial infection. They are uncommon. In other words, it seems that any one of these 3 lesions may be present in the pancreas in cases showing the typical clinical picture of acute hemorrhagic pancreatitis. In the majority of cases seen at operation or autopsy there is one large or several smaller areas of necrosis with a considerable amount of hemorrhage into the adjacent parenchyma.

Many workers believe that in most cases these various lesions represent stages of one fundamental pathologic process. Others consider the three lesions to be the result of different processes and classify this disease into three pathologic types on the basis of dominant lesion. Of the authors who consider these lesions to be stages in one process, some hold that hemorrhage is the fundamental lesion and that it causes the necrosis. Others^{24,62} hold that necrosis of the parenchyma is the primary lesion and that when the process causing necrosis involves blood-vessels, hemorrhage may occur. Almost all agree that if the patient lives long enough the process will localize and form an abscess. Likewise most workers agree that in some cases bacterial infection may cause suppuration and abscess formation which may or may not be accompanied by hemorrhage.

Rich and Duff⁶² believe that the primary lesion, except in cases due to bacterial infection, is a necrosis of the walls of blood-vessels involving chiefly the adventitia and media, which is difficult to differentiate from the arteriolar necrosis seen in the kidney in malignant hypertension. They feel that this lesion is characteristic in man and can be reproduced in animals by the digestant action of trypsin on vessel walls. Hemorrhage occurs due to rupture of the area of necrosis in the wall. The rest of the microscopic picture varies with the dominant gross lesion. There is usually an inflammatory edema of the gland with polymorphonuclear infiltration of varying degrees.

III. Clinical Observations Bearing Upon Etiology and Pathogenesis of Hemorrhagic Pancreatitis. *A. Relation of Acute Pancreatitis to Disease of the Biliary Tree.* Practically no one who had studied a series of cases of acute hemorrhagic pancreatitis has failed to point out the high incidence of chronic cholecystitis and cholelithiasis in these cases. This was noted by Fitz³⁴ in 1888 and has since been verified many times. Some of the more extensive studies which have been concerned with this factor are given in Table 1.

Thus, as Wangensteen, Leven and Manson⁷⁵ have stated, "clinically the common denominator . . . of acute hemorrhagic pancreatitis is associated disease of the biliary tract."

The majority of the studies in which this factor has been considered were presented before 1933, and they dealt only with cases of acute hemorrhagic pancreatitis. In light of these reports it is clearly established that, though the incidence reported by various authors varies in degree, it is certainly high in all of them. Dragstedt²⁴ and his coworkers have summed this factor up very well by stating that about 60% of cases of hemorrhagic pancreatitis in man are associated with chronic gall bladder disease. It is much less commonly associated with acute cholecystitis.

TABLE 1.—PUBLISHED DATA ON HEMORRHAGIC PANCREATITIS*

Author	Cases of hemorrhagic pancreatitis	Associated with chronic cholecystitis, %	Associated with cholelithiasis, %	Associated with acute cholecystitis, %	Normal gall bladder, %
Egdahl	105		42		
Gulecke	437		59		
von Schmieden and Sebening:					
Collected	1278	..	70		
Personal	38	..	81		
Eliason and North:					
Collected	232	71	66		29
Personal	14				
McWhorter	64	33	40	22	39
Fallis and Plain	26	57 7	60	15 4	26 9
Lewison	35	70	80	3	20

* Modified from Lewison.⁴⁴

B. Obesity has also been reported frequently to be a very common finding in acute pancreatitis.^{13, 21, 25, 28, 44} Since this factor is also common in disease of the gall bladder, its significance in acute pancreatitis is questionable.²⁴

C. It is likewise well established, that acute pancreatitis occurs commonly after the ingestion of a heavy meal,^{21, 25, 28, 44} and recently observers have noticed that it may also follow bouts of alcoholism.^{44, 62}

IV. Etiology of Hemorrhagic Pancreatitis. *A. Classification.* Lewison⁴⁴ modified McWhorter's⁴⁵ classification of the etiology of acute pancreatitis and presented a very complete survey of the factors which have been known to cause acute hemorrhagic pancreatitis, or which have been offered as theories of its etiology. This classification is made without regard to the relative incidence of the various factors, but is of value because of its all-inclusive nature. This classification with some modifications is as follows:

I. *Pancreatitis of Infectious Origin*

- A. Invasion of the pancreas along the lymphatics
- B. Invasion of the pancreas from the blood stream
- C. Infection by extension along the pancreatic ducts from the duodenum or from the bile ducts
- D. Invasion by direct extension from infected foci
- E. Invasion following activation of bacteria in the normal gland
- F. Invasion by bacterial spread through the walls of adjacent altered viscera

II. *Pancreatitis of Non-infectious Origin*

- A. Due to reflux into the pancreatic duct of:
 - 1. Bile—incident to
 - (a) Stone at ampulla of Vater
 - (b) Spasm of sphincter of Oddi
 - (c) Edema of ampulla of Vater
 - (d) Miscellaneous
 - 2. Duodenal contents
- B. Obstructions of the pancreatic ducts by:
 - 1. Epithelial metaplasia
 - 2. Miscellaneous factors as
 - (a) Tumors
 - (b) Stricture
 - (c) Edema
 - (d) Stone at ampulla of Vater
- C. Trauma
- D. Vascular accidents
 - (a) Embolus
 - (b) Thrombosis
 - (c) Rupture

III. *A Combination of Two or More Factors*

This classification will be followed in the discussion of the etiology of hemorrhagic pancreatitis.

B. Hemorrhagic Pancreatitis of Infectious Origin. That bacterial infection of the pancreas may cause the typical picture of hemorrhagic pancreatitis has been established by numerous autopsy reports of undoubted cases in which this has occurred.^{11,25,48}

1. *Rare Sources.* Cases due to hematogenous spread of infection are reported by competent workers.^{25,48} This is also true of cases due to spread of infection by direct extension from an adjacent infected focus.²⁵ However, it is generally believed that this is a rare occurrence. Its chief significance lies in the fact that the typical clinical picture of acute hemorrhagic pancreatitis can be produced by this means. It cannot be denied that infection by direct extension along the pancreatic ducts from the duodenum or the common bile duct may occur, but this lends itself less readily to verification and has not been clearly established. It seems certain that this, too, is a very rare cause of hemorrhagic pancreatitis. Invasion by bacterial spread from the walls of a distended loop of gut has been suggested,⁴⁸ but it likewise is rare, and in most instances would merely constitute a complication of peritonitis due to localization in the pancreas.²⁵ Statistically it is of little etiologic significance.

The question of activation of bacteria normally present in the pancreas was raised by Tower⁷² and elaborated by Dragstedt²⁴ in 1934. This problem requires further discussion but it should be considered under pathogenesis rather than under etiology.

2. *The Lymphogenous Theory.* The theory of lymphogenous spread of infection held a very prominent place in the discussion of the etiology

of hemorrhagic pancreatitis in the first two decades of the century. This theory found its basis in the frequent occurrence of chronic cholecystitis in cases of hemorrhagic pancreatitis. Maugeret^{49a} brought this theory into the limelight; Deaver,^{21,22} Sweet,⁷⁰ Graham,^{36a} and Judd^{41b} were its ardent proponents in this country. This theory held that acute (and chronic) pancreatitis is usually the result of bacterial infection of the pancreas and that this most commonly occurs by spread "over the anastomosing network of lymphatics in the retroperitoneal tissue which connects the gall bladder with the pancreas."³⁶

This theory was criticized by Archibald² on the basis that the spread of infection by this route would be blocked by intervening nodes and would demand retrograde flow of lymph. Sir Berkley Moynihan⁵³ countered this argument by postulating that chronic infection may well have blocked the nodes draining the gall bladder and this would cause a retrograde flow of lymph to the pancreas.

This controversy was highly productive and stimulated valuable investigations, but the lymphatic theory soon fell by the wayside. Kodama,⁴² in an excellent study, failed to demonstrate direct lymphatic connections between the gall bladder and the pancreas. Graham and his coworkers^{36a} accepted this work and withdrew their support of the lymphatic theory. Archibald² pointed out that cultures of peritoneal exudate are usually negative in hemorrhagic pancreatitis. Wangenstein *et al.*⁷⁵ presented convincing and rather conclusive evidence against the lymphatic theory. His arguments are as follows: 1, Necrosis of pancreas did not once follow the establishment of acute cholecystitis in animals; 2, direct injection of bacteria into the pancreatic parenchyma failed to produce necrosis; 3, in phlegmonous or gangrenous cholecystitis the complication of clinical acute hemorrhagic pancreatitis is unusual; the association with chronic cholecystitis is common. "If lymphogenous infection were the chief etiologic factor in hemorrhagic pancreatitis, we would certainly expect to see it more commonly with the acute form of cholecystitis, for it is well known that lymphangitis is common with acute infections and rare in chronic infections. Were this 'lymphatic theory' true, it would be difficult to explain the safety of conservative treatment of acute cholecystitis."⁷⁵

These arguments, plus the fact that cultures from the gland and peritoneal exudate are commonly sterile in hemorrhagic pancreatitis, have led Wangenstein, Manson and Leven⁷⁵ to conclude that "lymphogenous spread of infection very rarely may be held responsible for acute hemorrhagic pancreatitis."

In summing up the current concept of infectious origin of acute hemorrhagic pancreatitis, we may say that while infection, reaching the pancreas by various routes, may precipitate acute pancreatitis, this is an uncommon occurrence. If it does precipitate acute pancreatitis, the pancreatitis is usually of the suppurative variety,⁴⁴ but most authors agree that occasionally hemorrhagic pancreatitis in its typical form may result from infection.

C. Acute Hemorrhagic Pancreatitis of Non-infectious Origin. Turning to the non-infectious origin of pancreatitis we again find listed in the foregoing classification, factors which seem to have been proven to cause hemorrhagic pancreatitis, but which are responsible for only a very small percentage of cases seen in man.

1. *Uncommon Causes.* (a) *External Trauma.* External trauma to the pancreas is infrequent, but if moderately severe, it not infrequently is followed by acute hemorrhagic pancreatitis.²⁴ However, its total incidence is so small that it is responsible for very few of the cases reported in the literature. Its chief significance lies in the fact that it can produce the typical picture of acute hemorrhagic pancreatitis. Some workers⁷² believe that they have successfully utilized this method to produce hemorrhagic pancreatitis in experimental animals.

(b) *Vascular Accident.* Arterial embolism, and arterial and venous thrombosis have been reported as the primary etiologic factor found at autopsy in cases of hemorrhagic pancreatitis.^{25,46,67a} Tower,⁷² investigating this factor, found that she could regularly produce severe toxemia and death with the typical picture of acute hemorrhagic pancreatitis by tying off a sufficient portion of the blood supply to the pancreas in dogs. She questioned her own results because cultures of the peritoneal exudate were positive in all cases.

Dragstedt and his associates²⁴ state that the condition is not readily produced in animals by ligation of the blood supply to the pancreas.

Smyth^{67a} reported that the production of infarcts in the pancreas by intra-arterial injections of mercury resulted in local areas of necrosis, but in no case did he produce the typical spreading type of hemorrhagic pancreatitis.

2. *Reflux of Bile.* The common channel theory of Opie⁵⁵ holds that the great majority of cases of acute hemorrhagic pancreatitis are caused by the reflux of bile into the duct of Wirsung. This occurs when an obstruction, organic or functional, at the ampulla of Vater converts the common duct and the duct of Wirsung into a common channel. This theory found its origin in 1901 when, in performing an autopsy on Halsted's case of acute hemorrhagic pancreatitis, Opie found a small gall stone impacted at the ampulla of Vater converting the ductus choledochus and the duct of Wirsung into a common channel. Opie demonstrated that by pressure on the gall bladder, bile could be forced into the duct of Wirsung. From this finding and subsequent studies he concluded that the explanation for the common association of acute hemorrhagic pancreatitis and biliary tract disease is the occurrence of reflux of bile into the pancreatic duct, incident to an impacted calculus at the ampulla of Vater. His classic description of this autopsy attracted much attention and provoked a long series of valuable and enlightening experiments by many workers.

At the present time the common channel theory is the most common mechanism offered to explain the relationship of acute pancreatitis to chronic cholecystitis. It has been subject to much clinical and experimental investigation, and is now reasonably well established. However, the problems it has raised are not entirely settled.

The validity of this theory is absolutely dependent upon the proper anatomic arrangement of the entrance of the ductus choledochus and the duct of Wirsung into the duodenum. It is essential to this theory that the ducts unite to form an ampulla before they empty into the duodenum. This has been the subject of numerous investigations and some controversy.

A tabulation of results obtained by various workers investigating this factor is given in Table 2.

TABLE 2. —PUBLISHED DATA ON THE RELATIONS OF THE DUCTS AND THE AMPULLA OF VATER*

Author	No. of cases	Common ampulla, %	Cases in which a stone at the ampulla might form a common channel,	Cases in which the ducts emptied separately,
			%	%
Ruge	43	75		
Opie	100	89	30	11
Baldwin	90	78	..	32
Oser	100		32	
von Schmieden and Sebening	35		32	
Judd	170		4.5	
Mann and Giordano	200	..	3.5	
Cameron and Noble	100	74	66	
Belou	50	.	54	30

* Modified from Colp and Doubilet.¹⁸

Following discovery of the impacted calculus, Opie,^{55,57} in 1901, analyzed 100 autopsy specimens and found that a common opening into the duodenum existed in 89% of cases. However, he concluded that in only about 30% of these cases was the distance from the ostium to the apex of the ampulla great enough to allow the formation of a common channel by an impacted biliary calculus. Mann and Giordano⁴⁹ questioned the theory of biliary reflux, and reported that in only 3.5% of 200 autopsy specimens examined by careful dissection was it anatomically possible for impaction of a stone at the ampulla of Vater to convert the common duct and the main pancreatic duct into a common channel. Since all previous specimens had been examined by dissection after fixation, Cameron and Noble¹² attempted to study fresh material by more physiologic methods. They examined 100 fresh specimens by introducing a small biliary calculus into the ampulla of Vater and injecting colored fluid into the common duct. By this method they were able to demonstrate regurgitation of fluid into the duct of Wirsung in 66% of 100 routine autopsy specimens. This work has been generally accepted as answering the question conclusively. Thus, as Dragstedt²⁴ and others^{44,71,74} have stated, from this work we can reasonably assume that in 60% to 70% of cases the anatomic arrangement of these ducts is such that a common channel may conceivably be created.

Accepting this, it remains to be shown, as numerous workers have pointed out^{24,49,75} that bile will flow into the pancreatic duct if a common channel is created. Evidence bearing upon this question may be procured from several different sources and may be summarized as follows:

(a) *Evidence From Animal Experimentation.* Mann and Giordano⁴⁹ ligated the bile duct below the entrance of the pancreatic duct in a series of adult goats. They found that bile was not forced into the pancreas except after a considerable period of time, and that when it did infiltrate the pancreas under maximal physiologic pressure, acute hemorrhagic pancreatitis did not occur.

Bigard and Baker⁸ repeated the work of Mann and Giordano and found that hemorrhagic pancreatitis did result in very young goats but not in adult goats, indicating that reflux does occur in younger animals.

Wangensteen, Leven and Manson⁷⁵ produced a common channel in cats and found that bile passed into the pancreas. Since they found this to occur most regularly after a fat meal, they believed that contraction of the gall bladder was an important factor.

In 1931, Wolfer⁸⁰ produced a common channel in dogs by connecting the two ducts by means of a cannula, and found that pancreatic juice regularly flowed into the biliary tree.

Bottin^{8a} anastomosed the bile and pancreatic ducts in dogs and failed to produce pancreatitis.

(b) *Evidence of Direction of Flow in Man.* Numerous reports are available in which pancreatic juice has been demonstrated in the drainage from the gall bladder or the common duct. Some of these are as follows:

Bisgard and Baker⁸ reported a case in which pancreatic enzymes were demonstrated in drainage from the common duct. They concluded that this was not due to duodenal reflux because particles of dye and of charcoal fed the patient failed to appear in the drainage.

Popper⁵⁹ found an increase in amylase in bile (usually from the gall bladder) obtained at operation in 17% of 219 cases studied.

Colp and Doubilet^{18,19} found amylase in the biliary drainage in 4 of 14 cases operated for acute cholecystitis and in 10 of 35 cases of cholelithiasis or choledocholithiasis. They also reported that in 7 of 10 cases in which amylase was demonstrated, the duct of Wirsung was visualized by cholangiography.

Certain it is that pancreatic reflux into the biliary tree during external drainage of bile occurs in a considerable number of cases, and we are coming to realize that it is much more frequent than we had previously thought. Dragstedt²⁴ stated that external drainage altered the normal pressure relationships in the biliary tree so that flow into the common duct might be expected. Colp and Doubilet¹⁸ felt that in their cases, the pressure relationships could probably be assumed to be approximately normal because the bile flows against a resistance of 90 to 110 mm. of water (the height of the abdominal wall above the ductus choledochus) through the drainage tube. This argument would hardly be considered valid since the pressure in the human biliary tree has been shown to be much higher than this figure.^{54a}

(c) *Evidence From Autopsy Studies in Cases of Hemorrhagic Pancreatitis.* The bulk of direct evidence of the direction of flow in man consists of the numerous autopsy reports in cases of hemorrhagic pancreatitis in which bile has been found in the pancreatic ducts.^{25,37,55,56,57} Rich and Duff⁶² have questioned the validity of such evidence on the basis that pathologists routinely squeeze the gall bladder to investigate the patency of the common duct.

(d) *Evidence From Cholangiography.* Mirizzi⁵¹ in a study of functional disturbances of the bile ducts by cholangiography stated "one may conclude that reflux of lipiodol into the pancreatic duct seen on cholangiography is far from being mechanical and passive, but is rather due to the active phenomenon of a current from the biliary tree flowing into the pancreatic tree." He noted that at times the current seemed to flow in the opposite direction.

It seems plain that this evidence of the direction of flow in the com-

mon channel is conflicting and inconclusive. It seems obvious that the direction of flow at any one instant would depend upon the relative pressure existing in the two ducts. It is now fairly well established that the secretory pressure of the liver is about 25 mm. of mercury (Nash⁵⁴). The rôle of the gall bladder in this problem is unimportant because the maximum expulsive power of the normal gall bladder is never greater than the secretory pressure of the liver. However, the secretory pressure of the human pancreas is not accurately known. Mann and Giordano⁴⁹ have shown that in the dog the secretory pressure of the liver is less than 375 mm. of bile. Dragstedt *et al.*²⁴ found that the secretory pressure of the pancreas is about 570 mm. of water in the unanesthetized dog. The latter figure was obtained by a somewhat indirect method and cannot be accepted without question. The importance of this pressure factor depends upon the maintenance of a constant pressure within the two systems or exactly parallel fluctuations in the two pressures. It would seem more logical to believe that the relative pressures and hence the direction of flow in a common channel would depend upon the relative state of activity of the two organs at any one instant, and flow in both directions might occur in a period of time.

Dragstedt *et al.*²⁴ pointed out that if a patent duet of Santorini connected the duct of Wirsung with the duodenum, the secretory pressure of the pancreas would be nullified allowing bile to regurgitate freely into the pancreatic duet. Opie⁵⁵ found that the duet of Santorini anastomosed with the duct of Wirsung in 90% of 100 autopsy specimens. In slightly less than 50% of these cases, the opening of Santorini's duct into the duodenum was functionally adequate. Since there is no sphincter and the duodenal end of the duet of Santorini and the intraduodenal pressure is low, this factor may be important in determining the direction of flow in a common channel in some instances.

From this evidence we may safely conclude that the anatomic possibility of the formation of a common channel exists in a large percentage of individuals, probably 60% to 70%, and that there is direct evidence that this does occur in a considerable number of patients with biliary tract disease. There is clinical and experimental evidence that the flow in such a channel may occur in either direction. The relative incidence of the direction of flow and the factors governing it are not completely understood.

Accepting these facts, let us turn our attention to the factors which may operate to establish a common channel at the ampulla of Vater.

(c) *Factors Creating a Common Channel.* 1. *Stone at Ampulla of Vater.* The most obvious and plausible possibility of the formation of a common channel is that established by Opie's⁵⁵ classic autopsy—the impaction of a small biliary calculus at the ampulla of Vater.

Opie originally believed that this was the explanation of the majority of cases in which the common channel theory could be held responsible. However, it was soon noted clinically that a stone was not present in many such cases. Thus in von Schmieden and Sebening's⁵³ series of 1278 cases of hemorrhagic pancreatitis collected from German clinics, a gall stone at the ampulla was recorded in only 4.4% of cases. In this country, Fallis and Plain,³³ McWhorter,⁴³ and Lewison⁴⁴ have reported

9 cases of acute hemorrhagic pancreatitis in which a stone was found at the ampulla in a series of 125 cases. Hence, it is obvious that this factor can be implicated in only a small percentage of total cases of acute hemorrhagic pancreatitis.

2. *Spasm of the Sphincter of Oddi.* Archibald¹ suggested that the common and main pancreatic duct might be converted into a common channel by a spasm of the sphincter of Oddi, and presented evidence from animal experimentation to support his contention. This hypothesis arose from his observation that the sphincter of Oddi in cats was rarely overcome by hydrostatic pressures less than 600 mm. of bile. He introduced solutions containing iron into the gall bladder at pressures of 300 to 800 mm. of water and demonstrated by special stains that this solution had been driven into the pancreas by resistance of the sphincter of Oddi. In 1918, Archibald and Brow,² continuing this study, substituted bile for the iron solution and concluded that they could produce typical hemorrhagic necrosis of the pancreas by reflux of bile caused only by a resistance of the sphincter of Oddi. In these cases spasm of the sphincter was produced by the introduction of hydrochloric acid into the duodenum.

Wangensteen, Leven and Manson⁷⁵ in somewhat similar experiments in cats stated that they had been entirely unable to produce regurgitation of bile into the pancreatic duct in the absence of organic obstruction at the ampulla.

Previous to this Mann and Giordano⁴⁹ questioned Archibald's hypothesis on the basis of anatomic evidence. They pointed out that in order for spasm of the sphincter to form a common channel, both ducts must empty into a common ampulla—a condition they found in only 3.5% of 200 autopsy specimens—and that the sphincter must be located distal to the opening of the two ducts. They stated that examination of serial preparations of the sphincter in man demonstrated that this was not the case in most instances. They found that the usual position of the sphincter of the common duct was proximal to the termination of the duct and that the fibers of this sphincter not only surrounded the common duct but many of them also pass around the pancreatic duct, so that both ducts would be closed by spasm of the sphincter. They noted considerable variability in this region. In 1 case a considerable amount of the muscle tissue was distal to the entrance of the two ducts and partial contraction of the sphincter might have created a common channel. In another case all of it was distal to the duct orifices.

Boyden,⁹ studying the anatomy of the ampulla in man and in several species of animals, concluded that the usual arrangement is that while most of the fibers of the sphincter surround the common duct, the lowermost fibers surround the ampulla.

Archibald's theory has received very conclusive support in recent years by direct evidence obtained from postoperative cholangiography studies in man. This may be summarized as follows:

In 1935 Best and Hickens⁷ reported that "increased tonus and spasticity of the choledochoduodenal sphincteric mechanism" could be demonstrated roentgenologically by injection of radiopaque oils (lipiodol) into the biliary tree through a drainage tube in the common duct. This had been discussed previously under the name of "biliary dys-

kinesia" and various similar terms, but these authors, preferred the name "biliary dyssynergia," which they defined as a physiologic obstruction of the common duct. They demonstrated conclusively that the duct of Wirsung could be visualized due to reflux of lipiodol into it in a considerable per cent of cases of chronic disease of the biliary tract. Numerous authors have since reported studies verifying this work.

Colp and Doubilet^{18,19} compared the incidence of reflux into the duct of Wirsung on cholangiography with that of amylase in biliary drainage. They demonstrated filling of the pancreatic duct in the absence of organic obstruction in 20% of 37 cases studied. This occurred in 7 of 10 cases in which amylase was present in biliary drainage and in none of 25 cases in which it was absent.

Leven⁴³ studied this phenomenon in 91 patients and demonstrated reflux into the pancreatic duct in the absence of organic obstruction in 16 cases, and in 5 cases with obstruction due to a stricture or common duct stone.

Liedberg⁴⁵ reported 50 cases in which pancreatic reflux was demonstrated in this manner and studied the danger due to this procedure. He found pathologic diastasia in 8 of 50 cases.

Mirizzi⁵¹ concluded from experience with this method of study that reflux of lipiodol into the duct of Wirsung is a characteristic roentgenographic finding in the presence of "dystonia" (dyssynergia) of the sphincter of Oddi. He considered this disturbance to be functional in origin in the great majority of cases.

It is now fairly well established that when cholangiography is performed, the pancreatic duct is filled with lipiodol in about 20% of cases. This direct evidence establishes Archibald's theory of reflux due to spasms of the sphincter of Oddi on a basis that is difficult to refute. The relationship of this phenomenon to disease of the biliary tract is clearly demonstrated. Its implications as to the pathogenesis of pancreatitis are not yet completely understood, but certain it is that here is a mechanism which may produce reflux of bile into the pancreatic duct in a high percentage of patients with biliary tract disease.

3. Edema of the mucosa of the ampulla of Vater as an etiologic factor in hemorrhagic pancreatitis was advanced by Baló and Ballon⁵ in 1929. They presented 4 cases to illustrate that edema of the mucosa may occlude the orifice of the ampulla of Vater. In 3 of the cases the edema was due to cardiac decompensation and in 1 to dietary indiscretion followed by simple catarrhal jaundice. This factor may operate in some cases. It lends itself less readily to experimental verification, but must be included as a possibility.

4. Miscellaneous rare factors may, in isolated cases, occlude the ampullary orifice. With these we must consider carcinoma of the ampulla of Vater, stricture, the entrance of *Ascarides* into the orifice (50 cases recorded by von Schmieden and Sebening⁴⁵) and similar factors. Statistically such instances are of relatively minor etiologic significance.

Discussion. The so-called common channel theory of the etiology of acute hemorrhagic pancreatitis as an explanation for its relationship to chronic cholecystitis has been questioned by various workers. One of the lines of evidence offered against it has been the discovery at autopsy of cases of hemorrhagic pancreatitis in which the duct of Wir-

sung empties separately into the duodenum. In some of these cases there has been an associated chronic cholecystitis and cholelithiasis. Undoubted cases in which this has occurred have been reported by Simkins,⁶⁷ Dardinski,²⁰ and Rich and Duff.⁶² Such criticism is certainly valid, but it holds only for the case in question. That factors other than biliary reflux have caused hemorrhagic pancreatitis is unquestionable, but the common channel theory has not been offered as the cause of all cases of this disease. The occurrence of such cases does not constitute valid evidence against the common channel theory; it merely indicates that biliary reflux could not have been responsible for the case in question.

Likewise, until cholangiography furnished evidence that spasm of the sphincter of Oddi is common in biliary tract disease, direct evidence that chronic cholecystitis predisposed to the formation of a common channel, except in a small number of cases due to a gall stone at the ampulla of Vater, was very scarce. It had been postulated²⁴ that chronic inflammation of the biliary tract might alter the normal function of the sphincter of Oddi causing spastic contraction of part or all of it, but direct evidence was lacking.

The cholangiographic studies previously mentioned have produced some information which may raise further questions to the common channel theory. These studies^{18,19} indicate that reflux of lipiodol into the pancreatic duct occurs in about 20% of cases of chronic cholecystitis. Though the condition of the biliary tract at the time of these studies are made is quite abnormal, the findings suggest that reflux of bile into the pancreatic duct occurs in a much higher percentage of cases of chronic cholecystitis than does hemorrhagic pancreatitis. Thus Mirizzi⁵¹ feels, as a result of his experience with this method, that "in dystonia of the sphincter of Oddi one finds, on filling of the duct of Wirsung, that the duct is dilated and tortuous, and has a 'morphologic aspect' which indicates repeated increased tension in the duct, both because of stagnation of pancreatic secretions and because of reflux of bile." It is true that this is not based upon unquestionable evidence, but it does raise a question which should be investigated, because it strongly suggests that reflux of bile into the duct of Wirsung may occur many times without causing hemorrhagic pancreatitis.

It should also be recalled at this time that in 30% to 40% of cases of acute hemorrhagic pancreatitis, there is no concomitant disease of the biliary tract. It has been suggested²⁴ that a large percentage of these cases may be accounted for by the various other etiologic factors previously mentioned which have been shown to cause the disease in occasional cases. It is also possible that reflux of bile may occasionally occur in the absence of chronic biliary tract disease. This fact does not constitute a valid criticism of the common channel theory, though it has been held to do so by some authors.⁶²

Further criticisms of this theory have been made, but they are concerned more with the pathogenesis than with the etiology, and they will be discussed under that topic.

3. *Reflux of Duodenal Contents Into the Pancreatic Duct.* Reflux of duodenal contents into the pancreatic duct has been suggested by several authors as a cause of acute hemorrhagic pancreatitis. Williams and Busch^{78,79} thought that passage of a stone through the common

duct might leave the ampulla in such a state of atonic dilatation that duodenal contents might regurgitate into the pancreatic duct. Evidence in favor of this theory is the fact that cases have been reported by Dardinski,²⁹ Opie and Meakins,⁵⁷ and Simkins,⁵⁷ in which there was a hemorrhagic necrosis of the pancreatic parenchyma confined to the area drained by the duct of Santorini. In light of our present knowledge, such cases strongly suggest that regurgitation of duodenal contents into the accessory duct was responsible. Grant³⁷ suggested that since the orifice of the duct of Santorini is not protected by a sphincter, succus entericus might be forced into this duct by violent vomiting or reverse peristalsis. Dragstedt²⁴ criticized this idea for two reasons. He states that Pearce showed that it is nearly impossible to force colored fluid from the duodenum into the common duct or the pancreatic ducts. He also believes that, in vomiting, the increased intra-abdominal pressure would be transmitted equally to the pancreatic duct and the duodenum, and that therefore no pressure difference would result. This will be discussed further under pathogenesis.

4. *Pancreatitis Due to Obstruction of the Pancreatic Ducts.*—Several authors^{5,53,63,25,81} have suggested that simple obstruction of the pancreatic ducts, with damming back of pancreatic juice might result in hemorrhagic pancreatitis. It was usually felt that this would be more likely if there were bacterial proliferation in the retained secretions.

Rich and Duff⁶² are the most recent advocates of this theory, but they have discarded the necessity of bacterial infection. They hold that epithelial metaplasia in the duct system is the most common cause of obstruction and present autopsy evidence in support of this contention. These workers in an analysis of 24 cases of hemorrhagic pancreatitis at autopsy concluded that, in their experience, evidence of retrojection of bile was rare. They also stated that proven cases in the literature are scarce. They were able to demonstrate epithelial metaplasia in the ducts of 13 of 24 cases of hemorrhagic pancreatitis in routine sections and in 18.6% of 150 consecutive specimens examined by routine sections. From their investigations they concluded that "the majority of cases of hemorrhagic pancreatitis result from partial obstruction to the outflow of secretion, causing distention and rupture of acini and ductules behind the point of obstruction with resulting escape of pancreatic juice into the interstitial tissue. The rupture of dilated and thinned-out acini is particularly likely to occur during periods of increased pressure within the system, resulting from stimuli which greatly increase the production of secretion" (e. g., a large meal or the ingestion of alcohol). They felt that the fundamental etiologic factor is the release of pancreatic juice into the tissues due to rupture of ductules and acini incident to partial or complete obstruction of the pancreatic ducts. They considered that this obstruction, in the majority of cases, is due to epithelial metaplasia within the ducts and ductules. They conceded that retrojection of bile might be an occasional cause of hemorrhagic pancreatitis, but only when this results in rupture of ductules and acini.

That rupture of the ductules and acini may be a necessary factor has been supported by a few authors;⁴⁹ that epithelial metaplasia is the common etiologic factor has been either disregarded or doubted in

subsequent literature dealing with the subject. In discussing this, Lewison⁴⁴ stated that "Yotuyanagi (1937), in an exhaustive study, found epithelial metaplasia in 64% of normal specimens of pancreas. The frequency of this condition and the infrequency of hemorrhagic pancreatitis would oppose the premise of Rich and Duff."

Wangensteen *et al.*⁷⁵ reported that in one series of experiments they were unable to produce hemorrhagic pancreatitis by simple ligation of the duct, but when this was done and pilocarpine was injected subcutaneously they produced hemorrhagic pancreatitis in 3 cats.

D. Combination Factors in the Etiology of Hemorrhagic Pancreatitis. That a combination of factors, each of which is incapable of producing the disease alone, may often be responsible for producing hemorrhagic pancreatitis has been emphasized by Wangensteen *et al.*,⁷⁵ Dragstedt *et al.*,²⁴ Lynch,⁴⁶ McWhorter⁴⁸ and Lewison.⁴⁴

We have seen that the typical clinical and pathologic picture of hemorrhagic pancreatitis may result from a number of different etiologic factors. Thus infection, trauma, vascular accidents such as thrombosis, embolism, and rupture of vessels, reflux of bile and duodenal contents into the pancreatic duct have all either been proven to be cause of the disease, or have been implicated on the basis of clinical and experimental evidence as the primary etiologic factor. It also seems certain that in some cases a combination of these factors have operated to produce the disease. It is important to learn whether these diversified factors all operate through activation of a single mechanism, or whether different mechanisms are called into play to produce the ultimate effect.

V. The Pathogenesis of Hemorrhagic Pancreatitis. *A. Pathogenesis of the Local Lesion.* 1. The "trypsin theory." Since this pathologic picture occurs only in the pancreas and since varied etiologic agents are known to produce the same final result, it seems inescapable that some factor inherent in the pancreas is activated by various etiologic agents in such a way that it produces the lesions found in the organ. Because this gland secretes a digestive fluid that contains powerful enzymes capable of digesting all of the three great classes of food substances, it is logical to expect that one or all of these enzymes might be the destructive agent activated. Early workers^{55,56,57,63,64,78,79} considering the problem of pathogenesis, pointed out that while the starch-splitting and fat-splitting enzymes are secreted in the active form, trypsin, the powerful proteolytic enzyme, is secreted in the form of an inactive pro-enzyme and is activated in the duodenum by a specific activating enzyme secreted by the duodenal mucosa. These workers reasoned that such an arrangement must have been produced to prevent digestion of the pancreas by its own secretion. Because of these facts, it was accepted for many years that all etiologic factors produced the local lesions by intraglandular activation of trypsinogen, and that the powerful proteolytic ferment trypsin then digested the parenchyma of the gland.

This view was accepted almost without question until 1934, when Dragstedt, Haymond and Ellis²⁴ questioned it on the following basis: 1. "Since cell membranes are known to be composed largely of lipoids, should we not expect more destruction of cells from lipase than from the protein-splitting trypsin?"

2. The current concept of enzymes is that they are merely catalysts,

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These authors next turned their attention to mechanical factors in the production of hemorrhagic pancreatitis. They produced acute hemorrhagic pancreatitis, among them Opie,⁵⁵ Flexner and Pearce,⁵⁶ and many other investigators, by the injection of 5 to 10 cc. of bile into the pancreas of dogs. In a series of experiments, Opie and his associates found that hemorrhagic pancreatitis could be produced in dogs by the injection of 5 to 10 cc. of bile into the pancreas. In a series of experiments, Opie and his associates found that hemorrhagic pancreatitis could be produced in dogs by the injection of 5 to 10 cc. of bile into the pancreas.

Evidence was presented to show that the pancreas is the most susceptible of all organs to the cytolytic action of bile. This may be summarized as follows:

Sellards⁶⁴ injected 3 cc. of sodium taurocholate into the duct of the parotid and submaxillary glands and produced a fairly extensive necrosis of the gland. Comparing this effect with the effect of bile on the pancreas he concluded that the effect was similar to but not as severe as the effect of bile on the pancreas. This was confirmed by Dragstedt, Haymond and Ellis²¹ who also compared the effect of bile salts on the renal parenchyma with that on the pancreas and concluded again that the effect in the kidney was not comparable in degree to the effect on the pancreas. From this evidence Dragstedt, Haymond and Ellis concluded that "there is no doubt that the pancreas is more susceptible to

the local necrotizing effects of bile and bile salts than most other tissues."²⁴ To explain this increased susceptibility these workers assumed that it is probably in some way dependent upon the fact that the pancreas secretes enzymes capable of digesting all three classes of foodstuffs.

Since it is well established that the onset of hemorrhagic pancreatitis commonly occurs after a heavy meal when pancreatic secretion is maximal, and many workers have noted the production of the disease in animals by the injection of bile into the pancreatic ducts, these authors felt that pancreatic enzymes must facilitate the cytolytic action of the bile salts. Flexner³⁵ had shown that the destructive action of bile salts is inhibited by mucous and other colloid substances. Dragstedt *et al.* stated that it had been proven that normal serum protein protects red blood cells from the hemolytic action of bile salts, and that the protective property of the protein is completely destroyed by tryptic digestion.

On the basis of these facts Dragstedt, Haymond and Ellis²⁴ offered the following as a plausible explanation for the production of hemorrhagic pancreatitis by bile. Regurgitated or injected bile spreading through the duct system comes in contact with the cells of the pancreas and, due to the irritant action of the bile salts, parenchymal cells are injured and an exudate of serum or even frank hemorrhage occurs. "The initial attack of bile is repulsed"²⁴ by the protein of the exudate. Since these protective proteins are dead they are immediately attacked by the trypsin and polypeptidase of the pancreatic juice and by their digestive action bile salts are freed for further tissue destruction. These authors stated their conclusions on this matter largely in the form of questions; making clear that they were merely presenting an hypothesis. The questions are stimulating and the idea is well supported by the evidence cited, but it has certainly not been proven. It is well to recall at this time that these authors criticized the trypsin theory because there was no evidence that bile can activate trypsinogen, yet they have discovered no other means of activating it.

Moreover, we must remember that this can conceivably account for only those cases in which reflux of bile can occur. At best this mechanism could account for no more than from 60 % to 70 % of the cases of hemorrhagic pancreatitis which occur in man. Proven cases due to infection, trauma, vascular damage, etc., as previously stated, have occurred. Likewise authenticated cases in which the common and pancreatic ducts open separately into the duodenum, and cases in which the lesion was limited to the area drained by the duct of Santorini have been reported. Dragstedt, Haymond and Ellis recognized this and state that these factors are probably responsible for the 30 % to 40 % of cases in which bile could not be an etiologic agent. However, they have offered no statistical evidence for the statement, and they make no mention of the pathogenesis in these cases. If their theory is correct, are we to accept that some similar agent, aided possibly by trypsin, substitutes for bile salts in these cases? A comparable agent would be difficult to imagine in cases of arterial or venous thrombosis or embolism, or of direct trauma to the gland.

Experimentally acute hemorrhagic pancreatitis has been produced in animals by the injection of hydrochloric acid, sulfuric acid, sodium hydroxide, formaldehyde and a great variety of irritant substances.^{33, 35a, 55}

These agents may be considered comparable to bile salts, but these experiments are hardly applicable to the condition in man. The experimental production of the condition by the injection of active trypsin cannot be lightly dismissed in this consideration. Polya,⁵⁸ in an excellent study, reported that the intraductile injection of commercial trypsin in concentrations varying from 0.25% to 6% regularly produced the typical picture of the disease. This did not occur if comparable amounts of a solution inactivated by heat was used. Dragstedt, Haymond and Ellis noted that this and other similar studies had been criticized on the basis that the amount of solution used would traumatize the gland. Seeking to control this factor they injected 3 cc. quantities of active pancreatic juice into 3 dogs and failed to produce the lesion. It is pertinent here that few, if any, workers have produced the lesion with as little as 3 cc. of bile, but Polya felt that he had done so with 2 cc. of trypsin solution. In regard to the factor of the volume of solution, Flexner⁵⁹ injected 16 cc. of blood into the pancreatic duct of a dog without effect and Rich and Duff⁶² injected 10 cc. of trypan blue and of India ink without producing the lesion. Rich and Duff⁶² have confirmed the fact that intraductile injection of trypsin will produce the lesion in dogs. Since trypsin has been shown to be capable of producing the lesion alone on injection into the pancreatic duct, it certainly seems unwise to relegate it to the status of a secondary factor when bile regurgitates into the pancreatic duct.

Rich and Duff⁶² conducted an investigation of the pathogenesis of hemorrhagic pancreatitis which did much to reestablish the trypsin theory. In their autopsy study of 24 cases of acute hemorrhagic pancreatitis these workers concluded that they could demonstrate a constant and specific vascular lesion in the pancreas which was often indistinguishable from that seen in the kidney in cases of malignant arteriolar nephrosclerosis. This lesion is described in detail in their publication. It consists essentially of local necrosis of the wall of arteries and veins involving principally the adventitia and media. They then produced acute hemorrhagic pancreatitis in dogs by the injection of bile in 1 case, and of pure trypsin in 2 others. They concluded from microscopic study of the tissues that the same vascular lesion occurred in the pancreas of all 3 of the dogs and that it was indistinguishable from that seen in human cases. Believing that this was due to the direct action of trypsin on the vessel wall they injected 1 cc. of a solution of crystalline trypsin into the subcutaneous tissue of the abdominal wall of 5 dogs. They found this characteristic vascular lesion constantly present in the vessels of the subcutaneous tissue in the area of the injection. The lesion did not occur if the trypsin was heated, or if it was diluted 1 to 16 with saline. The injection of 1 or 2 cc. of sterile gall-bladder bile produced local tissue edema but no vascular necrosis or hemorrhage. They then injected sterile inactive pancreatic duct juice, obtained from the duct after stimulation of the pancreas, into the subcutaneous tissue and found that this produced the same lesion. From this they concluded that the vascular lesion was due to the direct action of trypsin on the vessel wall and that this could be produced by pancreatic juice containing inactive trypsinogen. The latter finding, they thought, might be explained either by the fact that the pancreas may secrete active trypsin under certain conditions.

- or that the activation of trypsinogen was initiated by the calcium of tissue fluids and carried on by products of tissue breakdown. From this and previously quoted etiologic investigations they concluded that "aside from the rare instances of primary rupture or occlusion of the pancreatic blood-vessels, hemorrhagic pancreatitis occurs only as a result of the disruption of the duct—acinar system with consequent escape of the secretion into the interstitial tissue of the gland." "If the escaping juice is rich in tryptic ferment and it comes into contact with arteries and veins, their wall will be destroyed, and extensive or localized hemorrhage will occur depending upon the size of the affected vessels."⁶² They felt that the widespread destruction of tissue seen in some cases is due to hemorrhage into the tissue and need not be blamed entirely upon the destruction of the parenchyma by trypsin.

Since this work was presented, but few additional studies of this aspect of the problem have appeared in the literature. These authors have presented very convincing evidence for the belief that trypsin is responsible for the local lesion, but it has not been recognized by all authorities who have subsequently written about the subject. A large portion of their work depends upon the interpretation of findings of microscopic examination of tissue, and as such, it should be confirmed before it can be completely accepted. Weiner and Tennant^{75a} found the vascular lesion described by Rich and Duff in some of the slides from the autopsies they reviewed. Smyth^{67a} found the so-called "trypsin lesion" in slides from 11 of 40 autopsies. He produced focal necrosis of the pancreas by injecting mercury into the artery to the pancreas, and found this lesion in 50% of the animals. From his study of this result he stated that the lesion was "limited strictly in all cases to the area of the infarct." He felt that this indicated that this lesion "is a result of or concomitant with the disease; it is not of etiologic significance."

It has been shown within recent years that small amounts of trypsin will coagulate blood, probably acting largely by converting prothrombin to thrombin, while larger amounts will produce the opposite effect by digesting fibrin.^{24a} This may be the explanation for the frequent finding of venous thrombosis at autopsy and an additional factor in the marked tendency to local hemorrhage which is so characteristic of the disease. Further implications of this information in the pathogenesis of the disease in question would at the present time be pure speculation.

Popper and Nechols⁶⁰ have recently reported some findings which should be considered at this time. These authors injected liver bile, gall-bladder bile and olive oil into the pancreatic ducts of animals in amounts varying from 0.1 to 3 cc. They found that in all cases a marked interstitial edema of the gland occurred very rapidly, and that a bloody exudate appeared in the abdomen within 1 hour. This occurred in 1 animal after the injection of as little as 0.1 cc. of bile. Most significant in this study is the fact that they could demonstrate a high concentration of amylase and lipase in the subcapsular edema fluid and in the exudate. It is unfortunate that trypsin was not injected because without that information the picture is incomplete. They did not produce hemorrhagic pancreatitis in any of these animals, but they did show that amylase and lipase had diffused out of the pancreatic ducts into the interstitial tissue and into the peritoneal cavity

in appreciable amounts. Were this true also for trypsin, one would expect that in diffusing outward this enzyme would have come in contact with vessel walls. The series of animals is too small and the studies are not sufficiently complete to provide any definite information which can be used in interpreting the work of Rich and Duff.⁶² However, it does suggest a method which should be of value in further investigating this problem.

. In summary, we can say that while the pathogenesis of the local lesion of acute hemorrhagic pancreatitis is not settled beyond question it appears that the release of active trypsin into the interacinar tissue is the factor of primary importance. If trypsin comes in contact with the wall of a blood-vessel it causes a local necrosis of the wall. This predisposes to hemorrhage, which furthers the process by damaging tissue and releasing more trypsin.

The criticism of this theory, offered by Dragstedt *et al.*, that no means for the activation of trypsinogen has been provided, and that there is no evidence that trypsin will damage living tissues seems to have been adequately answered by Rich and Duff's studies. This work has not yet been completely confirmed and hence cannot be accepted unreservedly, but as yet no serious objection has been raised to it.

Having considered the pathogenesis of the local lesion in acute hemorrhagic pancreatitis, let us now turn our attention to the available evidence bearing upon the cause of death in hemorrhagic pancreatitis. Here again we find that the principal contribution to knowledge of this problem has come from Dragstedt, Haymond and Ellis,²⁴ who have reviewed the literature on the subject up to 1934. Their work forms the basis of the following discussion, with additional data inserted where pertinent.

B. The Cause of Death in Acute Hemorrhagic Pancreatitis. 1. It has been agreed by practically all authors that the systemic picture produced by acute hemorrhagic pancreatitis is one of a very severe toxemia. Except for Egdaahl's²⁶ demonstration that extracts of necrotic pancreas are extremely toxic to animals, there is no direct evidence to support this statement. Dragstedt and his coworkers²⁴ felt we are probably justified in accepting the presence of a toxemia on the basis of verified clinical opinion because it has rarely been possible to demonstrate the presence of a circulating toxin in animals or in man.

Various authors have presented evidence that the toxic agent might be the trypsin contained in pancreatic juice, the products of autolysis or digestion of the pancreatic parenchyma, or bacterial toxins elaborated by bacteria proliferating in the necrotic pancreas.

Dragstedt, Haymond and Ellis²⁴ reviewed the experimental evidence which had been offered in support of these theories, and conducted extensive experiments in an attempt to solve this problem.

Sweet⁷⁰ reported a series of experiments in which he compared the toxicity of non-proteolytic and proteolytic pancreatic juice. He reported that his results confirmed the findings of earlier workers that non-proteolytic pancreatic juice was innocuous on intraperitoneal injection into animals but the injection of a comparable volume of pancreatic juice activated by succus entericus produced severe toxemia and death. He also demonstrated that intravenous injection of a mixture of pancreatic juice and succus entericus produced the picture of "pancreatic poisoning and death," but the inactive juice was innocu-

ous. On the basis of this finding, Sweet⁷⁰ felt that much of the systemic picture of acute hemorrhagic pancreatitis might be attributed to the systemic absorption of trypsin. Dragstedt *et al.*²⁴ criticized these and the earlier experiments, on the basis that the factor of bacterial contamination had not been adequately controlled. They injected 50 cc. of contaminated active pancreatic juice intraperitoneally into 1 dog and it died in 24 hours with no evidence of fat necrosis. Active pancreatic juice was sterilized by passage through a Berkefeld filter. This solution was injected into the peritoneal cavity of 3 dogs in amounts varying from 170 to 110 cc. No toxemia or fat necrosis occurred and the animal lived. This experiment was repeated using a large series of mice with the same results. From these results they believe that the toxemia of acute hemorrhagic pancreatitis could not be explained on the basis of the absorption of pancreatic enzymes from the peritoneal cavity.

The evidence for the belief that the absorption of toxic products formed in the autolysis or digestion of the pancreas might be the toxic agents in question consisted of experiments in which transplantation of the pancreas of 1 animal into the peritoneal cavity of another under strictly aseptic conditions resulted in toxemia and death of the donor animal.^{70,72}

Dragstedt, Haymond and Ellis²⁴ questioned these results because here too, despite aseptic precautions, the factor of bacterial contamination had not been ruled out. Tower⁷² had reported that she had successfully cultured bacteria from the normal pancreas in 15 of 16 dogs. Dragstedt and his coworkers verified this finding by obtaining positive cultures in 76% of 17 normal glands. These authors then repeated the transplantation experiments and 12 of 18 animals died. In 11 of the 12 animals that died they were able to culture an anaërobe "resembling, if not identical with *B. welchii*,"²⁴ from the peritoneal exudate present.

Sterile fetal pancreatic glands were transplanted into 1 dog with no ill-effects. They then autoclaved 4 glands and implanted them in the peritoneal cavity of 4 animals. The animals lived, and no evidence of systemic toxemia appeared. Muscle, liver and pancreatic tissue was sterilized and digested *in vitro* by sterile pancreatic juice. The toxicity of the sterile digestant mixture was compared with a similar contaminated digestant mixture by intraperitoneal injection in mice. It was found that the sterile digestant mixture uniformly produced no toxic effects, while in the majority of cases, the contaminated mixture was fatal.

From the results of this investigation these authors concluded that they had been unable to support the view that various fractions resulting from the digestion of the dead pancreas by activated pancreatic juice was responsible for the toxemia of hemorrhagic pancreatitis.

They then conducted what they considered to be an almost crucial experiment by implanting a sterile mixture of ground autoclaved pancreas and sterile activated pancreatic juice into the peritoneal cavity. No toxemia resulted. They felt that they had "proved conclusively that neither activated pancreatic juice nor the products resulting from digestion of dead pancreas within the abdomen by pancreatic juice are sufficiently toxic to produce the picture (of acute hemorrhagic pancreatitis) when bacteria commonly found in the intact pancreas are first removed."²⁴

2. *The Rôle of Bacteria.* From the experiments summarized above, Dragstedt, Haymond and Ellis²⁴ felt that "these bacteria are in some way necessary for the development of a toxemia in pancreatic necrosis." Though the nature of the toxic substances is unknown, these workers state that "it seems probable that the major amount of responsible poisons will be found among the relatively large group of toxic organic bases that are known to be produced from the decomposition of protein or of protein-split products by bacteria or their proteolytic enzymes."²⁴

Turning to the clinical literature these authors could find little positive support for this conclusion. They cite 3 cases reported in the literature in which a similar anaërobe was cultured. They felt that the current opinion that cases of acute pancreatic necrosis are sterile in man was due to failure of adequate careful bacteriologic studies, and suggested that such studies would contribute valuable information.

The status of the factor of bacteria in the clinical literature may be reviewed briefly at this time.

In the analysis of their questionnaire-collected data on acute hemorrhagic pancreatitis, von Schmieden and Sebening⁶⁵ reported that of 184 cases studied by culture, 103 were positive and 81 were negative. This is difficult to evaluate because of the nature of the study. Of 10 of their own cases, only 1 was positive and this may have been a contaminant. Except for isolated cases reported occasionally, other statistical studies previous to the work of Dragstedt *et al.*²⁴ contain very little evidence, positive or negative, bearing upon this question. Thus this factor is not even included in the series of 232 cases of Eliason and North²⁸ because data were not available.

Since this hypothesis of the essential part played by bacteria in producing the toxemia of hemorrhagic pancreatitis was reported, numerous authors have presented similar series of cases but none of them has contained an accurate, thorough bacteriologic study, so far as I can find. Most of the studies report that cultures had been taken in a small percentage of cases, and usually less than half of these were positive. Rich and Duff⁶² and others^{46, 67a} have stated that bacteria are not commonly seen on microscopic examination of sections through the necrotic areas of the pancreas in cases of this disease. Such studies as have been made have usually not included both aerobic and anaerobic cultures and their significance bearing on the point in question is consequently slight.

Some additional evidence in regard to the toxicity of the hemorrhagic exudate present in the peritoneal cavity should be considered. Whipple and Goodpasture⁷⁶ reported the hemorrhagic exudate found in the peritoneal cavity to be non-toxic. Irencus⁴⁰ confirmed this finding in experimental animals. He produced hemorrhagic pancreatitis in dogs and injected 15 and 30 cc., respectively, of the peritoneal exudate intravenously in dogs with no evidence of toxicity. He injected 2 to 3 cc. intraperitoneally in each of 10 white mice with the same results.

Popper⁵⁹ has shown that this exudate contains considerable amounts of amylase and lipase, but unfortunately it has not been analyzed for trypsin. However, this finding might also cause some question of the basic hypothesis that toxemia is a result of absorption of "proteinogenous amines" resulting from bacterial proliferation. Since this fluid is largely if not entirely formed by diffusion outward from the pancreas⁵⁹ it should be expected to contain such toxic substances picked up as it escaped.

Dragstedt and his coworkers²⁴ seem to have shown conclusively that.

in the absence of bacterial contamination, the presence in the peritoneal cavity of proteolytic pancreatic juice, of autolyzing pancreatic tissue, or of the products released by the digestion of pancreatic tissue by pancreatic enzyme, will not produce marked systemic toxemia in otherwise normal dogs. This evidence has cast serious doubt on the theories that the systemic effect of acute hemorrhagic pancreatitis in man may be explained by the absorption of trypsin or of protein-split products resulting from enzymatic digestion of pancreatic tissues.

At the present time, we see that there is very little direct evidence to support the alternate hypothesis proposed by Dragstedt and his co-workers. The experimental work reported by these authors furnishes only indirect evidence to support their conclusions, and for this reason they have proposed it only as an hypothesis. The factor of bacterial contamination certainly seems to have been established in their animal experiments, but there is little basis for its application to clinical cases. Direct evidence is not available to refute this hypothesis as offered, but it has certainly received no support from subsequent studies of the disease. A careful autopsy study in which both aërobic and anaërobic cultures are taken from necrotic foci in the pancreas is necessary to verify or refute the belief that toxic products produced by the proliferation of bacteria in necrotic foci in the pancreas is responsible for the systemic toxemia seen in the disease. It seems probable that there is a systemic toxemia in addition to the local lesion in cases of acute hemorrhagic pancreatitis but at the present time its nature and mode of origin of the toxic agent is unknown. The solution of this problem, which is probably essential if we are to reduce the high mortality of the disease, demands further investigations.

Summary. In summary we may say that the causes of acute hemorrhagic pancreatitis are varied and that many different factors may occasionally precipitate the disease. The most common cause is probably the reflux of bile into the pancreatic duct; most authors agree with Dragstedt, Haymond and Ellis²⁴ that this may be held responsible for about 60% of cases seen in the clinic. Of these, in possibly 10%, a common channel may be formed by lodgment of a small biliary calculus at the ampulla of Vater. In the majority of cases the common channel is created by spasm of the sphincter of Oddi, *e. g.*, biliary dyssynergia—incident to chronic disease of the biliary tract. Edema of the mucosa of the ampullary orifice and various factors may occasionally operate to create a common channel. Other factors such as vascular damage due to rupture of vessels, embolism or thrombosis, infection by various routes, and direct trauma are said to be responsible for at least a considerable portion of the remaining 30% to 40% of clinical cases. It has been held that anything increasing the pressure in the pancreatic duct to the point where ductules and acini are ruptured will produce this effect.⁶² There is some evidence that this may be due to simple occlusion of the pancreatic duct with subsequent strong stimulation of pancreatic secretion.

The pathogenesis of the local lesion is not completely settled. The principal controversial point is whether or not trypsin acting alone may produce the lesion by causing necrosis of blood-vessel walls and hemorrhage into the tissues; or whether, in cases of biliary regurgitation, bile salts by virtue of their cytolytic action are the fundamental factor in the production of the local lesion and that their destructive effect is

maintained by the action of trypsin on the protective protein of the inflammatory exudate. The bulk of the evidence seems to support the belief that the release of trypsin and its precursor into the interstitial tissues of the pancreas is the essential factor and that anything causing this to occur to a sufficient degree may cause the local picture.

Regardless of the pathogenesis of the local lesion, once it is present a profound toxemia results which is usually fatal. The nature of the toxic substance or substances is not known. It has been shown fairly conclusively that the toxemia is not due to the systemic absorption of elements present in activated pancreatic juice from the peritoneal cavity. There is excellent evidence to indicate that it is not due to the absorption of the products of autolysis or of enzymatic digestion of the dead pancreas, as has been the common concept for many years. It has been suggested on the basis of some indirect evidence that absorption of proteinogenous amines, formed by the proliferation in the necrotic tissue of bacteria present in the normal gland, is responsible for the toxemia.²⁴ This is not supported by the meager clinical evidence available but it cannot be denied at the present time. The solution to this problem may be the key to the existing high mortality of the disease. Further laboratory and clinical studies are clearly indicated.

RALPH JONES, JR.

AUTHOR'S NOTE.—Dragstedt, Haymond and Ellis²⁴ have presented a very comprehensive experimental study of this problem together with an excellent review of the literature to 1934. Rich and Duff²⁵ have reported an extensive study in 1936 and Lewison²⁶ has reviewed the literature to 1940. These papers should be consulted by any who care to pursue the subject further.

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OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

AND

H. P. WAGENER, M.D.

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

ANGIOID STREAKS OF THE FUNDUS OCULI

Any consideration of the subject of angioid streaks falls rather naturally into two periods, that before and that after 1929, the year in which

Groenblad⁹ called attention to the association between angioid streaks and pseudoxanthoma elasticum. In the 40 years between 1889, when the first case was reported by Doyme,⁷ and 1929, the available literature is concerned principally with case reports and theories as to the nature and origin of the streaks along with histopathologic descriptions of a few poorly authenticated cases. A total of 60 reported cases was collected by Holloway¹¹ in 1927. More than twice this number of cases have been reported since 1929; 139 cases collected by Scholz¹⁷ in 1941. Discussions during this second period have centered around the clinical relationships between angioid streaks, pseudoxanthoma elasticum, and osteitis deformans (Paget's disease) and the attempt to establish, through histopathologic studies, the systemic nature of the disease.

It is probably safe to say that, in spite of the rather considerable literature that has accumulated on this relatively rare condition, there has not been advanced as yet any explanation of the disease which has received universal acceptance. The uncertainty of the various observers from the ophthalmoscopic standpoint is attested by the numerous theories of the location and nature of the angioid streaks themselves. Holloway¹¹ listed a number of these which had appeared before 1927. Goedblad⁹ classified the theories under four headings according to whether they attempt to explain the streaks as products of the metamorphosis of hemorrhage, as anomalous or new-formed blood-vessels, as folds, or as ruptures of various layers of the retina or choroid. Holloway himself was inclined to consider Collins' explanation the most logical, *i. e.*, that the angioid streaks were produced by the deposition of hematogenous pigment, derived from repeated subchoroidal hemorrhages, in the perivascular spaces of the short ciliary arteries of the Circle of Zinn and of the branches proceeding from it. Indeed some form of the primary hemorrhage theory was favored by most of the authors prior to 1929. And as late as 1938, Clay⁶ stated that he had observed the development of angioid streaks in the area of a previously noted hemorrhage in the choroid. However, the general tendency today is to agree with the opinion of Groenblad that there is more evidence to support the view that hemorrhages occur after and not before the development of the angioid streaks.

Some authors have advanced the view that the streaks are not "angioid" but are actually vessels. According to Holloway, Oeller regarded them as retinal vessels and Schrader believed that they represented an anomalous arterial circle around the optic disk. The two most recent supporters of the vascular nature of the streaks have been Clay⁵ and Wassenaar.²² Originally (1932), Clay⁵ expressed the opinion that the streaks were short posterior ciliary veins, questionably anomalous, which had become thrombosed mechanically as a result of the increase of the fibrous tissue in the sclera with advancing age or in association with the degeneration of the elastic tissue of the sclera in patients with pseudoxanthoma elasticum. Later (1938) he seems to have adopted the view that some at least of the streaks may be new-formed vessels since he stated, as noted above, that he had watched a streak develop at the site of a hemorrhage and since he offered in support of his concept of the nature of the streaks a personal communication from Reese¹⁵ stating that he had observed in a microscopic section of an eye said to show angioid streaks ophthalmoscopically, a dehiscence in

a thickened lamina vitrea and over this, between the choroid and the retinal pigment epithelium, a fusiform-shaped fibrous plaque containing a blood-vessel (presumably new-formed). Clay states that the streaks must be blood-carrying channels since, when they are not too heavily pigmented, they can be made to disappear by pressure on the globe. On the other hand, as stated by Hughes,¹² an observation of Spicer's seems to prove definitely that the streaks do not represent a patent system of blood-vessels. In Spicer's case one of the streaks was interrupted by an area of complete atrophy of the choroid in which the sclera was visible and through which no connection could be traced between the distal and proximal portions of the streak. Wassenaar maintained that the peculiar course and branchings of the streaks could be explained only on the basis that they were actually vessels. He expressed the opinion that a congenitally weak or degenerated lamina vitrea might allow the penetration of vessels from the choroidal or posterior hyaloid system between the retinal pigment epithelium and the retina proper. The walls of such abnormally placed vessels would be especially vulnerable to injury or disease.

In evaluating any theory or explanation of the nature and origin of the angioid streaks, it must be remembered that, while the streaks are the most outstanding or diagnostically characteristic feature of the disease, yet there are ophthalmoscopically visible evidences that the basic lesion affects the tissues of the choroid and retina diffusely and certainly disproportionately to the number and extent of the streaks. Thus Groenblad calls attention to the characteristic changes in the macula and in the periphery of the choroid. In the macular region the earliest changes observed seem to be pigmentary disturbances resembling the punctate or granular myopic or senile degenerations of the macula. Later, hemorrhagic extravasations may take place. Still later transudative or exudative masses may develop associated with surrounding or irregularly placed hemorrhagic areas. The last stage is that of scar formation with atrophy of the choroid and pigment and connective tissue proliferation. One or more foci of choroiditis may be seen in extramacular locations in some cases. Occasionally retinitis circinata-like lesions may be seen. Often angioid streaks may be visible running into or under the macular scar. In the peripheral parts of the fundus, often especially temporal to the macula, there is characteristically a pigmentary degeneration of the choroid or retina giving rise to a rough granular mosaic-like appearance made up of a mixture of light gray, reddish, and brown or black spots. The angioid streaks do not extend into these zones of pigment degeneration. Commonly there is a grayish or yellowish-white zone around the optic disk with a bordering incompletely circular angioid or pigment streak. According to Groenblad, the streaks may be narrow and dark or broad and red and may vary in size in the same eye. In color they may vary from red to brown, gray or black. In an individual case, the streaks may change in color in the course of months or years, becoming either darker or broader and brighter, and may develop gray or white sheathing. They may increase in length or number. In some cases they may tend to disappear.

Proponents of the theory that angioid streaks are the ophthalmoscopic manifestation of folds in the retina or choroid are able to explain the diffuse lesions associated with the streaks on the basis of the primary pathology resulting in the secondary formation of the folds. But they

fail to account for the fact that the streaks appear to be an early rather than a late feature of the disease process. Verhoeff²⁰ and Law¹⁴ have presented histopathologic demonstrations of the presence of "folds" in eyes with angioid streaks. Verhoeff stated: "Microscopic examination of the eye showed the streaks to be ridges comprising the inner layers of the choroid, produced by cicatricial contraction of fibrous tissue which had replaced the deeper layers. The fibrosis involved almost uniformly about one-half the total extent of the choroid and was associated with extensive obliteration of the vessels and a few subchoroidal hemorrhagic extravasations. The cause of the fibrosis is obscure, but the most probable one would seem to be slowly progressive vascular obstruction limited to the affected area. Recurring hemorrhages within the choroid probably play a more or less important part in the process. To explain the vascular obstruction, the possibility of a congenital disturbance or defect in the innervation of the choroidal vessels is suggested. As a descriptive designation for the condition the term fibrosis choroideæ corrugans is suggested."²⁰

In the opinion of Law,¹⁴ angioid streaks are produced, in some cases at least, by a plication of the retina with an accumulation of pigmentary debris in the space formed between the rods and cones and the retinal pigment epithelium. In microscopic sections of an eye with ophthalmoscopically visible angioid streaks, Law found in the position of a streak a well-marked fold of retina. All the layers of the retina except the innermost and the outermost were involved in the plication. The internal limiting membrane of the retina passed over the fold in a gentle curve. The retinal pigment epithelium appeared to be undisturbed. Between the pigment layer and the rods and cones was an accumulation of extracellular uveal pigment and cellular debris. The lamina vitrea appeared to be intact and the choroid normal. Law did not offer a very definite explanation of the mechanism of the formation of the folds but he seemed to favor the occurrence of choroido-retinal hemorrhage as the initiating factor. He was inclined to consider this tendency to hemorrhage as part of a generalized vascular disease, probably of familial origin.

These explanations of the nature of angioid streaks revert to the original idea that the streaks are in some way the aftermath of preceding hemorrhage. This idea does not conform, however, to the present concept of the course of the disease which, as suggested by Wildi,²¹ may be divided essentially into three stages: 1, the appearance of angioid streaks and disturbance of the retinal pigment epithelium; 2, sudden subretinal exudation and hemorrhage in the macular region; 3, scar formation in the macula associated at times with the development of fresh hemorrhages in other parts of the retina. The anatomic explanation of the nature of the streaks, which seems to agree most logically with this presumed course of the disease and the only one which permits a logical etiologic association with pseudoxanthoma elasticum, is the theory, advanced originally by Kofler in 1917, that the streaks are actually ruptures in the lamina elastica, or lamina vitrea, of the choroid. Recently Hagedoorn¹⁰ and Boeck⁴ have published very extensive histopathologic demonstrations of these ruptures in the lamina vitrea and have attempted to reconstruct the ophthalmoscopically visible streaks on the basis of the microscopically visible fissures. Unfortunately, the reproduced streaks do not seem to fit in very accurately with the usual

course and location of the angioid streaks, as seen with the ophthalmoscope. And Verhoeff's objection to this explanation of the streaks may be a logical one; in 1926, Verhoeff and Sisson²¹ "described and depicted changes in Bruch's membrane essentially identical with those found by Hagedoorn in his case, including rupture of this membrane . . . in eyes without angioid streaks in patients over 47 years of age."

Hagedoorn gives a very elaborate description of the histopathologic changes observed in the study of microscopic sections of both eyes of his patient with angioid streaks. He states: "In studying the sections stained with hematoxylin and eosin one was struck by the confusing variety of pathologic changes; there was, however, one constant and dominating feature in both eyes: the pathologic condition of Bruch's membrane . . . it seemed to be considerably thickened and was overstained with hematoxylin . . . the membrane behind the equator showed a great number of defects, gathered especially around the disk. In the macular region the membrane was missing over considerable distances. Under high magnification the margins of most of the defects were as clearcut as though done with a knife. Therefore, it may be concluded that the defects were true ruptures of the membrane."¹⁰ Hagedoorn states also "It may be concluded that the described type of degeneration of Bruch's layer is specific for angioid streaks."¹⁰ In the sections examined by Hagedoorn the choroid appeared to be thickened and sclerotic with atrophy of the elastic tissue in some regions at the posterior pole. The walls of the choroidal arteries were hypertrophied and the internal elastic lamina was undulated and apparently normal. The retinal pigment epithelium showed evidences of degeneration, atrophy and proliferation. In certain areas, newly formed tissue containing elastic fibers and small new-formed vessels was present between the retina and the lamina vitrea. Hagedoorn concludes that "in angioid streaks a specific degeneration of the elastic system occurs at a time when other cells and tissues of the body still are in a good condition. New formation of elastic tissue is still possible, but evidently existing fibers do not reach the age of other tissues. This means a precocious senility of the elastic fibers, which view is supported by the fact that the degeneration occurs especially in regions in which the fibers are subject to continuous change in tension. It is possible that the mechanism of cellular and tissue metabolism which becomes defective in senility may become disturbed in an isolated specific tissue at an earlier age."¹⁰ This concept of the disease agrees essentially with that of Sorsby¹⁸ who classifies "angioid streaks" under the abiotrophies of the retina and choroid and suggests the name "elastosis dystrophica" for the systemic degeneration of which the angioid are a part. Apparently this name was also or originally suggested by Boeck.

In the sections of the eyes examined by Boeck, as in those examined by Hagedoorn, the most striking changes were found in the lamina vitrea of the choroid—diffuse and localized thickenings, changes in staining reactions, calcium deposits, and defects in continuity. In a flat reconstruction, these defects form long fissure-like lines resembling angioid streaks and also small round or oval holes. Over the smallest defects, the retinal pigment epithelium is unaltered and under them the choriocapillaris is normal. The defect in the lamina is filled with a structureless eosin-staining mass. This suggests that the primary lesion in angioid streaks is in the lamina vitrea. In connection with the larger

defects, the choriocapillaris is replaced by a fiber-rich, cell-poor connective tissue with few remaining capillaries but with some new-formed vessels which tend to grow out through the defect and between the lamina vitrea and the pigment epithelium, in association with some collagenous and elastic fibers. These new-formed vessels may be the source of the subretinal exudative and hemorrhagic lesions observed clinically. The defects involve apparently both the lamina elastica and the lamina basalis of the lamina vitrea. The defects may be due to actual degenerative holes as well as to mechanical tears in the diseased membrane. Circumscribed defects were observed also in the elastic lamina of a large choroidal artery. In the ciliary arteries extraocularly, there was destruction of the lamina elastica with connective tissue proliferation and with calcium deposits in the muscular and elastic layers. Degeneration was noted in the elastic tissue of the wall of the aorta in Boeck's patient as well as arteriosclerosis in other systemic vessels.

The histologic demonstration of the apparent primary involvement of the elastic lamina in eyes with angioid streaks furnishes a clue to the significance of the tendency to coexistence in the same individual of angioid streaks in the eyes and pseudoxanthoma elasticum in the skin, which tendency has been very definitely established clinically. Montgomery² describes the gross and histopathologic characteristics of the skin lesion known as pseudoxanthoma elasticum. The asymptomatic, discrete, chamois-yellow to orange papules which constitute the earliest recognizable phase of the lesion later assume a linear arrangement or merge to form plaques. The flexural folds of the skin soon become lax and stretched. The lesions are usually found first on the neck or in the axillae and may then spread to other parts of the body. Occasionally they involve the mucous membranes. Histopathologically, degenerative changes are found in the elastic tissue in the middle and deeper portions of the cutis, which may be either diffuse or in circumscribed nodules. The epidermis and upper portion of the cutis are not involved. A zone of normal connective and elastic tissue is present between the epidermis and the portion of the cutis which has undergone pathologic change. In the affected portion of the cutis there is edema and swelling of the elastic fibers followed by fragmentation and splitting of the fibers and later changes in their staining characteristics. Later, in the center of the lesion, there is curling of the fibers and granular and vacuolar degeneration of varying degree. The elastic fibers stain blue with hematoxylin or methylene blue. There are no changes in the cutaneous nerves. The changes in the connective tissue are minimal, edema and a tendency to homogenization of some of the collagen fibers. There is no or at most slight evidence of inflammatory change. An occasional blood-vessel is seen to have undergone slight dilatation or proliferation of the endothelium with or without slight perivascular infiltration of a few lymphocytes, plasma cells, and an occasional fixed connective tissue cell or mast cell. The elastica of the vessel walls remains intact. In 4 cases, stains for fats and lipids gave negative results. In 2 cases, detailed studies of blood chemistry revealed nothing abnormal. Montgomery² thinks that pseudoxanthoma elasticum can be distinguished definitely histologically from senile elastosis in which there is a marked degenerative change in the collagen as well as in the elastic fibers, a bluish staining of both with hematoxylin or polychrome methylene blue, and a merging of the two to form homogeneous masses. The papillary

bodies are involved usually in the process and there is atrophy of the epidermis and often of the cutis. Montgomery stated: "Absence of inflammatory reaction, together with the history obtained in many cases of more than one member of the family having the disease, makes it seem more likely that the condition is a malformation of elastic tissue and is probably on an hereditary basis."² It would seem at least possible that both angioid streaks and pseudoxanthoma elasticum are manifestations of a familial instability of the elastic tissues of the body.

Several authors, most recently Terry,¹⁹ Lambert,¹³ and Morrison¹⁵ have reported the finding of angioid streaks in the eyes of individuals with Paget's disease of the bones, osteitis deformans. Twelve instances of the association of these diseases have been reported in the literature to date. The significance of this association is not clear as yet. Terry examined the ocular fundi of 22 patients with osteitis deformans; 3 showed definite angioid streaks. Pseudoxanthoma elasticum has not been diagnosed as yet in a patient with osteitis deformans.

In most of the literature on this subject, the angioid streaks are regarded as the most essential part of the disease. Rayner Batten¹ has advanced a somewhat different concept of a disease of the choroid with rather protean manifestations of which the angioid streak is only one and not a necessary one. In summary, Batten stated that this choroidal disease has its onset in middle life about the age of 40. It is primarily a vascular disease, often familial and probably hereditary. The earlier symptoms are pallor around the disks, fine pigment changes at the macula, and angioid streaks without necessary loss of vision. The later symptoms include central macular hemorrhages and exudation with retinitis circinata, extensive choroidal atrophy, scattered gross pigmentation, and retinitis proliferans with or without angioid streaks. Batten elaborates on 7 principal points: 1, This familial disease of the choroidal vessels is characterized in its early stages by angioid streaks and other pigmentary changes of the choroid and retina and later by gross central choroidal hemorrhages and the resultant scars. 2, The disease is of slow onset and extends over many years. Attention may be called to its presence first by the sudden occurrence of gross hemorrhage, commonly at the macula, of choroidal or subhyaloid type. 3, It is a primary disease of the vessel walls, not secondary to any septic or inflammatory disease. It may be associated with a similar vascular weakness in other parts of the body either in the same individual or in other members of the family. 4, The angioid streaks are due probably to a slow seepage from the choroidal vessels and are not an essential part of this familial choroidal disease. 5, Some hitherto unexplained types of retinal pigment degeneration at the macula and of choroidal pigmentary degeneration may be other manifestations of this disease. 6, This choroidal disease may account for many of the hemorrhages occurring in the macula and other parts of the fundus without demonstrable etiology. Retinitis circinata occurs frequently in this disease as a phase of the macular hemorrhage stage. 7, There is lack of definite information as to the after-history of these cases. But it seems probable that, after the subsidence of the acute hemorrhagic phase, there may not be much progression and the patient may not go on to blindness. Because of the frequent later development of hemorrhagic lesions, a guarded prognosis should be given to patients who present only angioid streaks at the time of initial examination.¹

In view of the many conflicting views and findings presented, to all of which certain objections may be raised, it must be admitted that the problem of the nature, origin and significance of angioid streaks is not settled as yet. It is barely possible that, in spite of the rather uniform and characteristic ophthalmoscopic appearance of the streaks, basically different choroidoretinal pathologic lesions may be concerned in their formation. In this connection, it may be well to note the report made by Benedict³ on the microscopic study of an eye which probably presented angioid streaks in the fundus before enucleation. Benedict stated: "Microscopic examination of these sections, however, failed to show any pathologic changes that could be identified as angioid streaks. The retinal structures appeared practically normal, except for numerous small vacuoles resulting from fixation and embedding. The retinal vessels were patent and showed no sclerosis. There was no retinal hemorrhage. The choroid showed perivascular lymphocytic infiltration about many of its vessels and heavy deposits of pigment surrounding the vessels and nerves. Sclerosis and obliteration of the choroidal vessels were not seen. The veins were large and thin walled; the arteries were all patent and their walls were not thickened. The lamina vitrea was regular except for a few very small hyaloid nodules. There was some fibrosis of the choroid, but folding or projections of the inner layer of the choroid were not present. . . . In the hematoxylin stained sections there was no evidence of increased calcium in the choroid or the lamina vitrea. . . . There were no thrombosed vessels about the zonule of Zinn . . . nor were there any abnormal vessels. . . . Rents in the pigment epithelium . . . could not be confirmed."³

In October, 1941, Scholz¹⁷ published a review of the literature on angioid streaks in which he gave some interesting data. He collected a total of 188 cases. Of this number, 66 had been reported from Germany, 60 from the United States, 17 from Great Britain, 14 from the Scandinavian countries, 9 from France, 8 from Japan, and 6 from South America. Six of the cases were in negroes and 6 in Japanese; the rest were in whites. Of the patients, 58% were males and the age incidence peak was in the fifth decade. Loss of vision was noted in 63% of the cases. The color of the streaks was noted in 103 instances; it was said to be brown or reddish-brown in 65, gray in 27, and red, black, white, or grayish-brown in the remainder. Lesions were found at the macula in one or both eyes of 140 patients; recent hemorrhage in 35, scarring in 19, abnormal pigmentation in 18, and, in the remaining 23, hole, exudate, disciform degeneration, retinitis circinata, or some other form of retinitis. Hemorrhage in the retina was described in 65 cases and choroiditis in 70. Among the 139 cases reported since 1929, pseudoxanthoma elasticum was found to be present in 59% and was specifically stated to be absent in 13%. The diagnosis of osteitis deformans was made in 9% of the patients. Senile elastosis was noted in 5 cases (3.6%). Scholz quotes Sandbaek-Holstroem to the effect that among 100 cases of pseudoxanthoma elasticum reported in the literature, the presence of angioid streaks was noted in 87. According to Scholz, of the patients in whom the lesions in the fundi had been observed for more than a year, the angioid streaks were noted to have increased in number in 33%, to have decreased in 10%, and to have remained unchanged in 56%.

HENRY P. WAGNER, M.D.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 15, 1942

Vascular Reactions: (1) During Shock; (2) Following Removal of Large Amounts of Blood. RICHARD G. ABELL and IRVINE H. PAGE (Department of Anatomy, University of Pennsylvania, and Lilly Laboratory for Clinical Research, Indianapolis City Hospital). Shock was produced in rabbits and cats by two methods: 1, the incomplete ligation of all 4 legs (1 rabbit and 14 cats); 2, crushing one taped leg (3 rabbits). Three criteria were used in attempting to determine whether the animals actually went into shock. These were: 1, blood pressure measurements; 2, hematocrit determinations; and, 3, the appearance of the viscera at autopsy. Blood pressure measurements showed a gradual and persistent fall in pressure which dropped below 60 mm. Hg and remained there for an hour or more before death in 12 of the 14 cats in which direct recordings were made. Hematocrit determinations on 3 cats showed hemoconcentration of moderate degree, readings rising in a typical instance from a control of 36% to 45%. Autopsies usually showed the presence of small hemorrhages in many parts of the body, especially the heart, liver, spleen and lungs. The rabbit and 13 of the cats died, in all but 2 instances from 3 to 8 hours after releasing the ligatures. Of the 14 cats, 4 were nephrectomized, 3 adrenalectomized and 2 pancreatectomized.

The vessels studied were in transparent intestinal-mesenteric chambers (Zintel, H. A.: *Anat. Rec.*, 66, 437, 1936). The animals were anesthetized with 30 mg./kg. pentobarbital, injected subscapularly in the rabbits and intraperitoneally in the cats. Microscopic observations of the arteries and veins of the mesenteries showed that marked arterial constriction occurred early in shock and usually persisted until an hour or so before death. The veins also became narrowed. With the constriction of the arteries and veins there was a noticeable decrease in the amount of blood going to the intestine and mesentery, as shown by blanching of these structures and decrease in venous return. The same

vascular reactions occurred in shock which was produced by incomplete ligation of the legs following the removal of both kidneys, or of both adrenals, or of the pancreas. No such reactions occurred in the vessels of the mesentery of a control cat.

The effect of hemorrhage on the mesenteric vessels was studied in 3 cats. Following withdrawal of from 32 to 60 cc. of blood, the arteries of the mesenteries constricted and the veins became narrowed, as previously noted in shock.

In 1 rabbit, anesthetized with 30 mg./kg. pentobarbital, the arterioles in a transparent moat chamber (Abell, R. G., and Clark, E. R.: *Anat. Rec.*, 53, 121, 1932) in the ear were studied during shock. Arteriolar constriction persisted for 3 hours and was then followed by relaxation.

No narrowing of any of the vessels was observed in the mesentery of a cat following destruction of the brain and spinal cord by pithing.

These experiments indicate that in rabbits and cats the terminal stage of shock (produced by the almost complete occlusion of the circulation of the 4 legs for 3 hours, or by crushing one taped leg) is preceded by an intense and prolonged arterial constriction. In the cats this was shown to occur regardless of the presence or absence of kidneys, adrenals or pancreas.

A detailed account of the experiments with the cats is in press (Page, I. H., and Abell, R. G.: *J. Exp. Med.*).

The Influence of Season and Temperature Upon the Oxygen Consumption of the Sand Crab, *Emerita Talpoida* Say. G. A. EDWARDS (The Edward Martin Biological Laboratory, Swarthmore College, Swarthmore, Pa.). The oxygen consumption of the sand crab at rest was measured in summer and winter, using animals of various sizes and of both sexes. The life span of *Emerita talpoida* from the Woods Hole region was determined and it was found that the females lived about 27 months and the males about 25 months. The adult female has a carapace length of 25 mm. and the male 15 mm. In summer the animals were found distributed over the whole beach but in winter the shores are often frozen and the animals were found away from the shore under 6 to 12 feet of water. Growth and activity are maintained throughout the whole year.

The oxygen consumption of the smaller animals was greater than that of the larger animals per unit of weight and at any given temperature. The effect of rising temperatures upon the metabolism was greater in the smallest weight class of animals and least in the largest animals.

Sudden changes in temperature of 10° or less from the normal brought about rapid changes in the oxygen consumption, but the effect was such that the oxygen consumption became normal immediately when the animals were returned once more to the initial temperature. Greater changes had an effect such that the animal lost the ability to return to the normal oxygen consumption again.

The oxygen consumption of both the winter and summer animals increased with increases in temperature until heat injury set in and then decreased. The maximum oxygen consumption in summer was at 26° C., that in winter slightly lower. The oxygen consumption in winter was greater than that in summer at temperatures below 17° 10

20° C. The thermal death point in summer was approximately 10° higher than that in winter.

It appears that *Emerita talpoida* from the Woods Hole area becomes adjusted with season in such a manner that the metabolism in winter is kept up toward a level comparable to that during the warm summer months. The winter acceleration of metabolism coincides with the preservation of growth and activity at low temperatures.

The Respiratory Reactions to Hypoxia in the Normal Unanesthetized Dog. A. H. CHAMBERS, GEORGE BREWER, H. W. DAVENPORT and SAMUEL GOLDSCHMIDT (Department of Physiology, University of Pennsylvania). Respiratory minute volume, rate, and tidal air were measured on normal, unanesthetized dogs breathing oxygen concentrations ranging from 16% to 4%.

Minute volume increased to a maximum value within the first 3 to 6 minutes, then fell off to a plateau level maintained throughout the experimental period. With 16% or 14% oxygen the plateau may fall back to control (outdoor air) level, while rate may remain unchanged. In all cases, the initial increase in minute volume was accomplished by increased tidal air rather than rate, while the fall to the plateau was accompanied by decreased tidal air and increased rate. At all times, tidal air remained above control value. With 4%, 5% or 6% oxygen a second increase in minute volume characterized by an increased rate and maintained tidal air, occurred following the initial increase. In long experiments such increases may be repeated several times.

While breathing room air following 20 minutes' exposure to low oxygen minute volume fell to a value 50% to 70% of the control. Tidal air at this point decreased below control value and rate, if previously increased, fell to or slightly below control.

Absence of apnea following loss of CO₂ during the previous hyperpnea suggests a stimulating factor produced during hypoxia which can maintain the respiration.

A few long experiments using 4% oxygen were done to determine the point of failure of respiration. This time ranged from 40 to over 155 minutes. Respiration ceased before the heart failed. Resuscitation by artificial respiration failed in only 1 case.

The Respiratory Reactions to Hypoxia in Dogs With Deafferented Carotid and Aortic Receptor Areas. HORACE W. DAVENPORT, GEORGE BREWER, ALFRED H. CHAMBERS and SAMUEL GOLDSCHMIDT (Department of Physiology, University of Pennsylvania). Three unanesthetized dogs deprived of their chemoreceptors were made to breathe air-nitrogen mixtures in which the oxygen percentage was from 18% to 9%. At the beginning of the period of hypoxia their minute volumes decreased from 15% to 27%. The decrease was relatively independent of the degree of hypoxia. With increasing hypoxia the tidal air at the point of maximum depression decreased below the control, and the respiratory rate increased. The maximum depression occurred earlier the lower the oxygen percentage. Following the depression the minute volume increased to or above the control and was maintained high throughout the rest of the period of hypoxia. The increase above the point of maximum depression increased with increasing hypoxia.

During the increase the tidal air rose toward the control level, and the rate increased. Both changes were proportional to the degree of hypoxia. When the dogs again breathed air their minute volumes remained greater than the control for at least 10 minutes.

The results are interpreted to mean that during hypoxia central depression of the respiration and some sort of central stimulation exist coincidentally. The depression and stimulation increase with time and with hypoxia, and after the end of hypoxia they decay slowly. The respiration represents the algebraic sum of the depression and stimulation. The stimulation is quantitatively greater and is responsible for the maintenance of a high minute volume despite the existence of depression.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this *Journal* to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the *Journal of the American Medical Association* with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, i.e., that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold an opinion” gives the more exact meaning.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES

VASOMOTOR AND OTHER REACTIONS TO INJURIES AND
VENOUS THROMBOSIS*

By JOHN HOMANS, M.D.

CONSULTANT IN SURGERY, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

IN recent years, a number of vascular reactions in the arms and legs, hitherto of seemingly mysterious origin, have come to be understood. They are of several sorts. There are local constrictions of large arteries and peripheral spasms in various parts of the vascular bed on one side or the other of the capillaries. With all these, pain is associated and with some of the more serious, ischemia. Cyanosis, edema and atrophy of the tissues are familiar features.

Not all such states appear at first sight to be related to one another. For example, Volkmann's contracture, as a complication of fractures near the elbow, would seem to have little in common with a painful femoral thrombophlebitis, and neither appears to be related to the causalgias, traumatic edemas and other complexes due to wounds of great nerves, and to such a variety of minor injuries as dog bites, fractures and blows. Yet all these and other disorders probably result from injury to or irritation of the tiny nerves which attend the blood-vessels. At least these tiny nerves appear to initiate not only local constrictive spasms but a variety of remarkable reflex disorders, and by supposing that many such vicious reflexes pass into the spinal cord and out again, involving in their course the sympathetic system, a number of disabling and previously unconquerable states have become at least understandable and sometimes curable. In such a broad conception as this, one must not be ashamed of setting up an hypothesis which can hardly be proven, and of taking false steps at times, provided the

* Trimble Lecture presented before the Medical and Chirurgical Faculty of the State of Maryland, April 29, 1942, Baltimore, Md.

main line of thought is productive. Progress can be made and false steps retraced as they are noticed. That, I believe, has been the conception of that very fascinating and imaginative Frenchman, René Leriche,⁸ who, more than anyone else, has preached the significance of what may be called the "vascular nerves." These are loosely called sympathetic nerves, but all are not sympathetic in the strict sense, since some are sensory and, passing centrally, leave the blood-vessels to join the somatic nerves through which they enter the spinal cord. However, in that capacity which interests us here, they are linked with the sympathetic or out-flowing, vasomotor system and may therefore be counted a part of that system. In fact, even though all are not vasomotor nerves, they are concerned with some very common vasomotor reactions.

I am going to begin by showing you how closely the vascular reactions of thrombophlebitis are related to the vascular reactions of various injuries. It is an old observation, for many years neglected, that thrombophlebitis of the lower limb, the inflammatory thrombosis which has been called "milk leg" and which the laity simply dubs "phlebitis," is very rarely a cause of gangrene of the leg: I remember running into an observation of this sort in the writings of Cruveilhier,² the great French surgeon-pathologist, who, in his day, made very valuable observations upon the vascular system. Before I became familiar with the subject, I supposed that such gangrene, in patients very sick with typhoid or pneumonia, was actually due to arterial embolism or to an unusual necrosis of bacterial origin, which is now no longer seen. Today, of course, it seems highly probable that it was consequent upon an extensive, spasmodic obliteration of the femoral artery. Many accounts have appeared during the last 5 or 6 years, especially in the French literature,^{4,8,9,10} of violent arterial spasms of this sort, some of which have relaxed spontaneously while others have resulted in complete ischemia and gangrene. One account describes a surgical exploration of the femoral vessels which revealed an extensive thrombosis in the vein, beside which lay an insignificant, tiny, contracted femoral artery. The operator, Grégoire,⁴ punctured it with a fine needle to discover that there was still a faint arterial flow through the vessel, and secured momentary relaxation by an injection of procaine about the arterial wall. However, the artery soon relapsed into uncontrollable spasm and the leg became gangrenous. I, myself, have observed in one instance a gangrenous affair of this sort, not proven by exploration but supported by clinical evidence, and in another case have been able to observe a patient in a very early stage of the arterial spasm, assure myself by a procaine block of the lumbar sympathetic that the peripheral vessels of the limb were capable of a normal vasodilatation and note, some hours later, complete relaxation of the artery associated with an excessive flow of blood into the whole leg. Evidently the contraction finally relaxed of

its own accord. I have belabored this point in order to show you that there is such a thing as a definite local spasm of a large artery, associated with thrombophlebitis in the companion vein.

Presumably, in such instances, the cause of the spasm lies close to the artery, in the form of an inflammatory reaction involving the vasomotor nerves serving the walls of both vessels, a *local* disorder.* For if the spasm resulted from a spinal reflex, touched off by irritation of the central-going sensory filaments serving both the artery and vein, the resulting reaction should not be local but generally distributed through the whole vascular system of the limb. I will return, later, to the *generalized* peripheral spasms which are associated with thrombophlebitis and which are clearly of reflex origin, but these are not in question here.

A similar local arterial spasm occurs as a result of acute injuries involving the tissues close to the arterial wall. This became known, during the last World War, as arterial stupor, and there are excellent accounts describing the passage of a bullet close to the femoral artery, which in one instance (Kroh, 1915, 1917^{6,7}) was seen to have shrunk into a tiny needle-like structure, a cause of numbness, coldness and complete loss of power in the extremity. Spasm of this sort is capable of relaxing spontaneously but, if it does not relax, it may lead to a very serious situation because the collateral vessels, which may also have been thrown into spasm, are rarely able to take care of the peripheral circulation when the principal vessel is strongly contracted. Recently, it has been suggested that Volkmann's contracture is an affair of this sort. A violent trauma to the region of the lower arm, elbow or forearm, particularly the sort which causes a supracondylar fracture, has often been followed by a contracture of the muscles of the forearm, making a claw of the hand and ending in incurable fibrosis of the muscles, nerves and blood-vessels. Though Volkmann himself finally regarded the contracture as ischemic, it has since been thought that the disorder is due to an acute passive hyperemia resulting from a tense blood clot in the region of the fracture, a serious situation, which is aggravated when the arm is placed in acute flexion or when splints are applied. It is much more likely, as I have said, that the condition is really one of arterial spasm. Griffiths⁵ strongly maintains this view, and a very interesting account of an exploration in an early case of supracondylar fracture was given some years ago by Montgomery and Ireland.¹⁵ Seeing the contracted vessel, not itself injured, lying in traumatized tissue, they refrained from further manipulation and were able to report that in the next few days the vessel gradually recovered from its spasm, so that some weeks later the fragments could properly be replaced. It is easy to

* In this I differ, perhaps, from Ochsner and DeBaakey¹⁸ who picture all vascular constriction in the limb of thrombophlebitis as being reflex in nature. The difference need not be taken too seriously.

believe that both the local vasospasms of thrombophlebitis and injury are due to the irritation of perivascular nerves, probably of the actual vasomotor, or sympathetic, sort.

I now come to another kind of vasoconstriction which is also associated with both injury and thrombophlebitis. Although this sort is so little understood that both its mechanism and situation are not exactly known, it appears to be due to a reflex excited by a sensory stimulus, one which passes inwards, presumably into the cord, and out again, by way of sympathetic channels. For the most part, this constriction shows itself widely in the periphery of the involved limb. Its effects, in the form of pain, paresthesia, edema and cyanosis, may be observed in unexpected instances after blows and fractures, after bites by animals and infected wounds from thorns, to cite a few of many instances, a state which has been called "minor causalgia" because, although it resembles in some respects the serious variety described by Weir Mitchell,¹⁴ it is far less violent. A very similar disorder is occasionally associated with an inflammatory thrombophlebitis. The leg is left, after the acute stage of the disease, in a painful state of slight cyanosis, edema and paresthesia, identical for practical purposes with the causalgia-like condition so unpredictably brought on by trauma. A traumatic minor causalgia may be forced upon any limb but is most common in the arm, particularly in the hand, and is favorably influenced by blocking the sympathetic nerves to the part. One need only inject a few cubic centimeters of procaine into the region of the gangliated chain serving the arm or leg to abolish for the moment all signs of the disease, both subjective and objective. There are other ways of breaking into some part of the reflex arc, though repeated treatments may be required to effect a cure, and in some instances all methods fail. This is true alike for the postphlebitic and post-traumatic states. It is fairly clear that in postphlebitic minor causalgia the perivascular nerves of the iliac and femoral vessels are involved in an inflammatory reaction and that in the post-traumatic state, the nerves of the finer blood-vessels are irritated. Until some better hypothesis is offered, one must suppose that the sensory nerves serving the blood-vessels carry toward the spinal cord stimuli occasioning these reflex disturbances.* Figure 1 shows how impulses may arise from the tiny fibers attendant upon the blood-vessels, including those of the great nerves. De Takats⁷ has drawn one figure illustrating the course of reflexes from the joints as well.

* There is a good deal of confusion as to the course of such reflexes. The afferent sensory neurons whose cells lie in the posterior root ganglia have branches serving the arterioles. Antidromic impulses (axon reflexes) from these neurons cause peripheral vasodilatation as exhibited in the familiar flush of painful injuries. But since cyanosis and edema, that is, signs of peripheral vasoconstriction, are associated with the states here described, it would seem that the reflex actually travels into the cord and touches off sympathetic activity.

So far, I have attempted to show that both large and small vessel vasospasms may result from thrombophlebitis and from a great variety of injuries. I believe that now I should review some anatomic and physiologic considerations. All blood-vessels, of course, are in

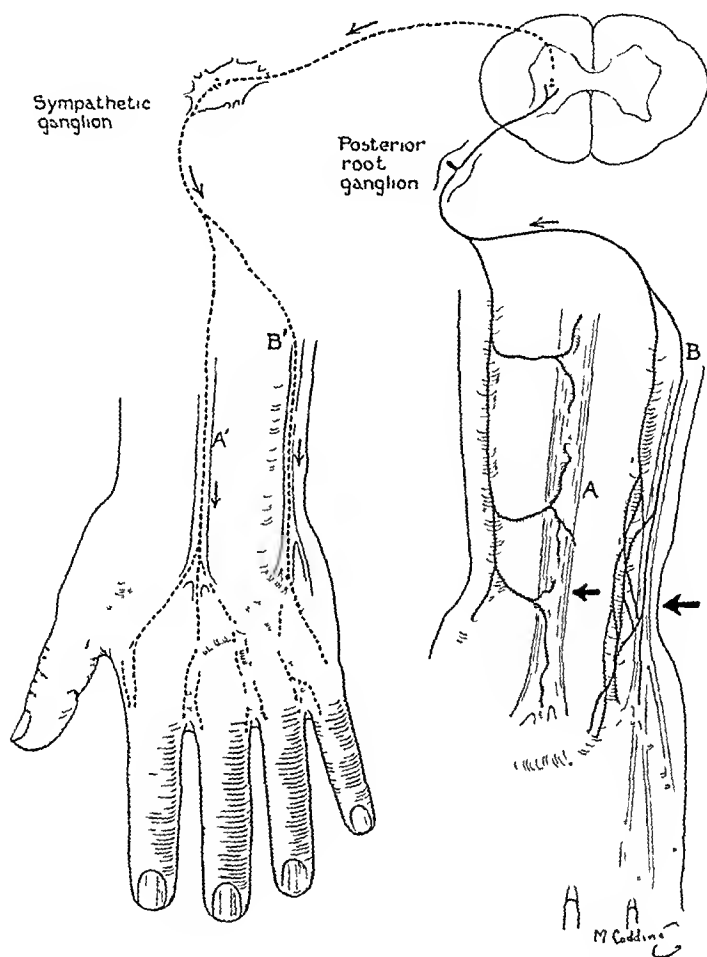


FIG. 1.—*Minor causalgia*: Diagrammatic sketch showing the course of a reflex starting from the sensory filaments of the blood-vessels (right) and causing vasoconstriction in the arterioles (and venules?) of the fingers (left). In the forearm on the right, the size of the great nerves and vessels is exaggerated. Each heavy arrow points to a supposed region of injury, whence the sensory filaments of the blood-vessels start the unnatural reflex. A, Median nerve, showing the sensory filaments of its rich blood supply. B, Ulnar nerve and artery. Filaments from the ulnar artery pass to the ulnar nerve and so to the cord. A', Outflowing reflex sympathetic vasoconstricting impulses in the median nerve of the same hand being distributed to the fine blood-vessels of the fingers. B', The same impulses distributed through the ulnar nerve. Notice especially the smooth, slightly edematous fingers, without knuckle markings as contrasted with the normal thumb, a very common feature of minor causalgia. The radial and median distribution of sympathetic impulses might equally well be affected, leaving a normal ulnar field.

a state of vasomotor tonus. All are in some degree elastic. All relax when vasoconstrictor impulses are removed, though whether there actually are true vasodilator nerves appears to be somewhat uncertain. And all, except the very largest arteries, are capable of

being contracted with a good deal of force when their sympathetic supply is irritated. Sympathetic stimulation, then, causes vasoconstriction, and sympathetic paralysis causes vasodilatation. These reactions, which are directed from centers in the hypothalamus, medulla and cord are brought about especially by *cold* and also by emotional excitement of various sorts. When there is a need for conserving heat, the peripheral vessels are caused to contract and the skin ceases to allow heat to escape. On the other hand, when heat must be dissipated, the superficial vessels dilate and various other cooling agencies are put to work. But vasomotor reflexes have yet other important effects. If a great artery to a limb is cut off, the branches of the arterial tree serving that limb tend to dilate, permitting a collateral circulation to become established. Unfortunately, this is not a very well protected reaction because if a great artery, instead of being divided, is injured or becomes thrombosed or even is occupied by an embolus, the whole arterial tree, instead of dilating, contracts, so that a collateral circulation is greatly restricted. Apparently, this latter unfortunate reaction is a reflex one and can be overcome only by actually dividing the vessel or the structures immediately about it. Here again is evidence of impulses running centrally, which if unimpeded, call forth an outgoing sympathetic stimulus which contracts the branches of the great vascular tree but whose interruption permits a corresponding vasodilatation. That this contraction is not due to a local irritation of outgoing sympathetic nerves is suggested by the known distribution of sympathetic constrictor fibers to the arterial system of any limb. These constrictor fibers do not run for great distances along the vessels but reach them at successive levels. They emerge from the somatic nerves to be distributed to the arteries in a series of branchings, and in the end, the distribution to the peripheral parts corresponds roughly to that of the sensory nerves to the skin. If then, the sympathetic nerves supplying, for example, the femoral artery in the region of the groin, are stimulated, a vasoconstriction in the local area served by these nerves will occur, but the peripheral vessels will remain unconstricted since those are served by sympathetic fibers which have not yet passed out upon the arterial tree from the great somatic nerves. In other words, local stimulation or paralysis of vasomotor fibers causes a relatively restricted, direct reaction.

Not only are the outgoing vasoconstrictor nerves distributed to a succession of vascular fields, but as Moore and Singleton¹⁶ have found, sensory fibers accompanying the arteries and veins of a limb leave these vessels somewhere—no one knows at what intervals—to join the somatic nerves and pass within them to the posterior roots of the spinal cord. Very likely, these sensory nerves are associated in a great part of their course with the strictly sympathetic vasoconstrictor fibers, but they always end by entering the cord

through the posterior roots, just like any other sensory fibers. It results that irritation of the sensory filaments attendant upon a blood-vessel at any point is capable of sending into the central nervous system impulses which may result in a reflex disorder affecting the circulation in the whole limb. The extent of the reaction appears to be uncertain and variable, but at least it tends to be general. There may even be a spill-over to the opposite limb. Thus, you can readily see the difference between the effect of a local vasomotor stimulation and a local sensory stimulation. The former is local; the latter is more or less general. Probably the two sorts often occur simultaneously. Perhaps I can bring out these differences by citing details in some of the states I have so briefly described.

Localized Arterial Spasm. There may be included in this category the arterial spasm secondary to acute thrombophlebitis and to injuries such as fractures or wounds by missiles. But there are yet others: There is the spasm of the brachial artery related to the passage of the brachial plexus over the first or a cervical rib. There is acute arteritis, an inflammatory reaction of the arterial wall. And finally, there is a very remarkable state of spasm due to embolism.

Arterial Spasm in Acute Thrombophlebitis. Acute thrombophlebitis is the inflammatory sort which obstructs a large vein such as the femoral and its continuation, the external and common iliac. With this disease, there is often a very considerable exudative reaction about the wall of the vein and strangely enough, about the artery as well. It even seems as if there must be some common cause for the exudate about the 2 vessels, such as a lymphangitis. But in any case, whether or not a perivascular inflammatory reaction is present, the venous thrombosis is associated, in occasional, unpredictable instances, with localized arterial spasm (Fig. 2). A clinical sign of this is the pain experienced by the patient, a pain sometimes so severe as to be agonizing. An individual may even suddenly fall to the ground when attacked by the pain and the sudden shutting off of the arterial supply to the limb. As already explained, the spasm may relax spontaneously or it may continue and lead to an actual thrombosis and finally obliteration of the principal artery. Gangrene is extremely rare, but temporary loss of the peripheral pulsations is not very uncommon, and weakening of the pulse in the dorsalis pedis artery is of frequent occurrence.

It is not my purpose to describe in detail the treatment of this condition. A sympathetic paralysis, such as can be brought about by blocking with procaine the lumbar sympathetic chain, is unlikely to relax the really dangerous local spasms of the main artery. However, all methods of inducing relaxation should be employed, that is, procaine sympathetic block, the application of heat to the body and groin, and possibly the vasodilating drugs. In less serious cases, a diffuse *peripheral* vasospasm—of the arterioles, venules or

both combined—overshadows such gross spasm of the great artery as may be present. It will soon be described, and I only speak of it here to offer you a better picture of the leg in femoro-iliac thrombophlebitis. A moderate degree of spasm in the great vessel, often associated with this peripheral vasospasm, is probably relaxable by a sympathetic procaine block.

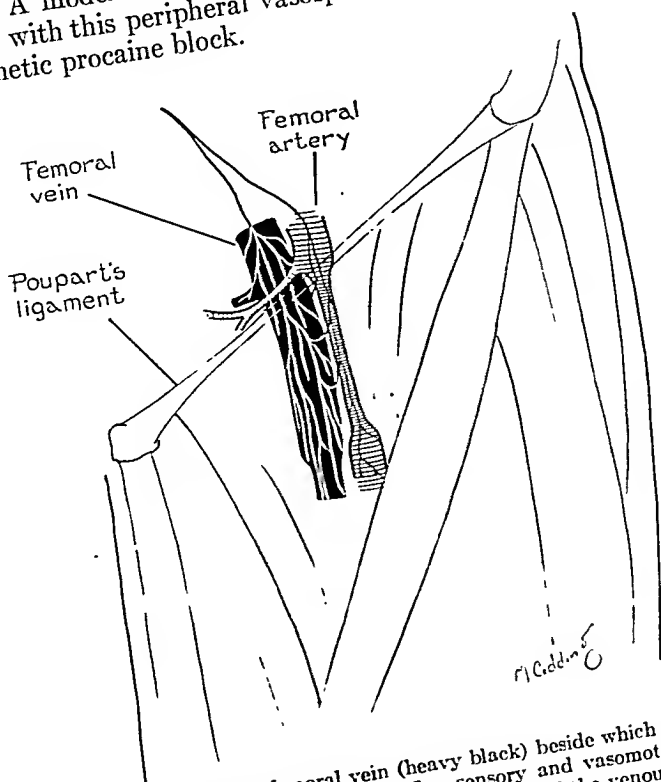


FIG. 2.—The thrombosed femoral vein (heavy black) beside which is a constricted femoral artery. The distribution of the fine sensory and vasomotor nerves lying upon both vessels is intended to suggest that irritation of the venous group may be communicated to the arterial probably directly. Local irritation of the vein's wall causes a local spasm of the artery.

Arterial Spasm Due to Fractures and Wounds by Missiles. I have no personal experience with this type. Probably all arteries smaller than the common iliac are susceptible to this accident, which has perhaps most often been reported as occurring in the femoral. Apparently there is no essential difference between spasmodic closure due to the near passage of a bullet and that due to a small hematoma in or about the arterial wall or pressure by a fragment of bone, as in Volkmann's contracture. An analysis of that disorder shows that hemorrhage into the tissues is seldom excessive, nor need splints or a plaster cast have been applied. In fact, acute passive hyperemia does not seem to be a factor. Clinical observations show that pallor of the skin and weakening of the radial pulse, rather than venous hyperemia, usher in the disease, which is not to say

that local pressure about the fracture may not contribute to the circulatory failure in some cases. The necrosis of muscle which so rapidly leads to the fibrosed, clawlike arm of Volkmann's paralysis comes on very rapidly; release of pressure by removal of dressings and extension at the elbow influence it very little and exploratory incision has many times revealed arterial spasm. This spasm much resembles that of arterial embolism, for constriction of the collateral vessels is associated with it. And consistent with Leriche's⁸ observations that resection of a contracted obstructed artery is the best way to open up the collateral circulation of the ischemic limb, arterial resection has proved curative more often than any other procedure.

The Scalenus Syndrome and Spasm of the Brachial Artery. Irritation of the subclavian artery or the lower cord of the brachial plexus by the first or a cervical rib have come to be known as the scalenus syndrome. The observations of Adson and Coffey¹ and of Naffziger¹⁷ have suggested that the vessel and plexus, one or both, may become compressed between the rib and the scalenus anticus muscle. When circulatory symptoms predominate, the subclavian is very rarely thrown into spasm. It is more apt to be dilated, the actual spasm being beyond in the brachial artery which may in time become thrombosed and fully obstructed, giving rise to a cold, numb hand. A very ingenious explanation of this brachial spasm is offered by Telford and Stopford,²¹ who suggest, on the basis of Todd's anatomical observations, that vasoconstrictor fibers destined for the brachial artery may be irritated in the lowest cord of the brachial plexus by rubbing of the first rib against the nerve. Such an hypothesis is consistent with clinical experience and has seemed to me to derive support from a rather dramatic event a few years ago upon the baseball field.

An ageing pitcher made a difficult, hurried throw in a strained position from near third base to first. In a few minutes his arm "went numb." It was then discovered that though a good axillary pulse was present, the brachial pulse was obliterated and I believe has remained so. A fair collateral circulation must since have developed, however, as the athlete continued during the following year to pitch with fair success. May this not be the acute form of such a sympathetic irritation?

Arterial Embolism, irrespective of the obstruction caused by the embolus itself, calls forth a high degree of arterial spasm. That this spasm involves the whole arterial tree beyond the obstruction is now recognized, and that such widespread spasm is the cause of excruciating pain is highly probable, as the following incident shows:

A middle-aged man suffered a sudden pain in his left arm. At the same moment, a pulsating lump appeared above the left clavicle. Before the significance of this association was realized, the lump disappeared and a long tender thickening replaced the left radial artery, which ceased to pulsate. At once the fingers took on a rather cadaveric color, especially the little and ring fingers, which became flexed upon the palm. Pain was

agonizing. The patient guarded the fingers from the lightest touch. Any attempt to extend them was bitterly opposed. The contracture actually resembled that of Volkmann. No cause for embolism being known, a diagnosis of "arteritis" was made and the radial artery was explored under procaine. For a distance of some inches, it was greatly thickened and appeared inflamed. Accordingly, the abnormal portion (then discovered to contain a long embolus) was excised; whereupon the patient was at once dramatically relieved. Not only did all pain disappear but the fingers could now be moved and freely handled. Warmth and color improved. Of course, the explanation is that an embolus, of cardiac origin, had entered the subclavian where it caught for some hours and then passed on to become jammed into the radial, exciting a violent spasm in that vessel and its branches.

A similar relief may be observed when an embolus is removed from a great artery such as the femoral. Evidently, irritation of the arterial wall by the sudden distention of the impacted embolus calls forth the useless, violent, painful local and general reflex vasospasm in the affected limb.

Arteritis. Since this rare condition is sometimes regarded as of traumatic origin, I will say a word about it here, though there are good reasons for holding it to be a result of infection. *Periarteritis nodosa*, that strange and fatal disease, offers one form. *Thromboangiitis obliterans* offers another. As to the latter, there is no knowing whether thrombosis precedes the granulomatous lesion in the arteries and veins or the granulomatous lesion precedes the thrombosis. In either case, something goes wrong with the wall of the blood-vessel. There is beginning to appear evidence that the fungus infection of the feet play a part in the disease and that tobacco is a contributing feature. Trauma often touches it off. Perhaps an allergic factor is of importance.

Other forms of arteritis are associated with acute infections. One of the most specific is arteritis of the temporal artery. The temporal vessels become inflamed and tender. Headache is severe and signs of a general infection of a subacute, even recurring sort, are evident. The local lesion is reminiscent of *thromboangiitis obliterans*. Possibly the arterial wall reacts in a similar way to a variety of harmful influences.

Vasoconstriction of the Small Blood-vessels: Minor Causalgia. Of all the vascular disorders this is the most baffling and the most fascinating, for it is related to pains and disabilities which cause great suffering and economic loss, which tend to become fixed upon individuals otherwise well and which, at the same time, depend upon reflexes of a most unstable sort. The exciting injury often seems too trifling to have caused so much trouble, and the relief of the condition is sometimes absurdly simple, sometimes irritatingly difficult. The whole matter is concerned with the mechanism of pain. Sensory stimuli are so influenced at their source that they become painful, a matter with which the peripheral circulation is somehow concerned. I have used the term "minor causalgia" for

the symptom-complex here discussed. Actually the pain is not the burning pain of Weir Mitchell, but since the term "causalgia" has come to mean a serious functional disorder associated with injuries to nerves, it may perhaps be applied to a similar though minor ailment.

This is not the place to discuss the nature and mechanism of Weir Mitchell's causalgia, which results from partial injuries of the great nerves of the limbs. It would appear to be a gross distortion of the normal reaction to a painful injury, but whether it results from an unnatural accumulation of Sir Thomas Lewis' hypothetical H-substance and a consequent wide sensitization of his nocifensor nerves or, as Leriche⁹ maintains, it is merely the "spontaneous creation of a particular variety of vasomotor temperament, which we cannot even yet distinguish," is impossible to say. In any case, there is a peripheral *vasodilatation* in the major form of causalgia by contrast with the obvious diffuse vasoconstriction of the minor disease with which I am familiar and which alone is under discussion here. Instances of what I hold to be minor causalgia are the following:

A. M., a stout, unmarried woman of 20, was first seen 10 months after an injury to the right hand. The base of the thumb, in the region of the thick adductor muscles, had been pinched from front to back in a piece of heavy machinery. Neither skin nor any bone was broken. Soon the patient developed a very sensitive spot—"trigger point"—on the back of the hand where the pinch had occurred and at the same time the surrounding region upon the thumb and forefinger became "numb." The patient was unable to make a fist, partly owing to pain occasioned by any movement and partly owing to a peculiar sort of stiffness common to these cases. She had several times gone back to work, handling light machinery, but each time had had to give up. There was some spontaneous pain which the patient confused with the pain of attempted use of the thumb and hand.

There was present an area of numbness to pin-prick confined to the back of the thumb and adjacent hand and a small area of hyperesthesia to light touch between the base of the thumb and forefinger. Deep pressure here was intolerable. Infiltration of this sensitive region with procaine solution gave considerable relief, which, however, hardly lasted overnight.

A paravertebral procaine sympathetic block for the arm at once restored the hand to normal. The numbness and sensitiveness disappeared. One could handle the thumb vigorously and the girl could make a tight fist for the first time in 10 months. The relief lasted only 48 hours but successive blocks lengthened the free intervals. Six injections were given in the next 5 weeks. Then, after a 3 months' period of freedom, there was a partial recurrence. One more procaine block took care of this, since when, for over a year, the patient has remained well, though she is probably incapable of strenuous work.

E. J., a married woman, 44 years of age. About 2 years before I saw her, some splinters of wood had entered her left little finger. Infection followed and an operation to establish drainage resulted in a sinus. The 2 terminal phalanges and, subsequently, the proximal one, were successively removed without securing healing. About this time, pain became serious. The ulnar side of the hand, particularly the amputation stump and the region of a sinus above it, turned a deep lilac color. The skin of this area appeared macerated and gave off the characteristic odor of dead tissue. Here there was moderate hypersensitiveness, but higher up, the palmar surface of the forearm was

dull to pin-prick. The remaining fingers were a little bluish but the change was mainly in the ulnar field. The patient was becoming a morphine addict. She was emotionally unstable, cried over trifles and was nearly unmanageable.

Two sympathetic block showed that pain could be relieved and the cyanosis greatly improved. But though pain was now controllable and further improvement seemed certain, an ulnar periarterial sympathectomy was thought to offer a more rapid cure, especially since the lesion was so nearly confined to the ulnar field. The effect of the operation was dramatic. Pain was permanently abolished; the cyanotic color disappeared from all but a small area about the sinus, and within 6 months the patient had voluntarily returned to work. The sinus did not actually heal, however, for almost a year.

Here, of course, is a much more serious disorder than the pinch at the base of the thumb. Successive operations, performed without appreciation of the peculiar local reaction, fixed the causalgia more firmly with each procedure. The general effect upon the patient's morale was more like that of a major causalgia. A fascinating feature was the immediate and permanent relief of pain by a perivascular neurectomy—presumably of sensory nerves.

I could describe many similar cases with variations. All have a family resemblance. There is always an area of paresthesia which usually occupies the back of the hand and often shows a roughly anatomical distribution. For example, it may be confined principally to an area served by the ulnar and median nerves (Fig. 1). There may or may not be a sensitive "trigger point." There is usually some slight cyanosis and enough edema nearly to obliterate the wrinkles on the knuckles. The grip is weakened. Atrophy of bone (Sudeck's atrophy) is often discovered by recourse to the Roentgen ray but is not essential to the diagnosis. The most characteristic features are the pain, the relative insensibility to pin-prick, the cyanosis and slight edema, and a feeling of stiffness in the fingers and wrist. If these features can be abolished at once, *i. e.*, in a few moments, by a successful procaine block of the sympathetic supply to the limb, the diagnosis is fully established. The patients are usually delighted and surprised by the effect, with which the imagination has nothing to do. One may predict failure without altering the completeness of relief.

One can never fail to be struck by the persistence of relief for hours, days, weeks or life, after a block with 1% procaine which can maintain a sympathetic paralysis for no more than 15 minutes to an hour. Even more remarkable is the relief by local infiltration of the sensitive area which is so often present. I, myself, have had a little experience with this method of treatment, but Livingston, who has made an intense study of the subject, has cured many patients by local injections of procaine into the trigger point or about the sensory nerve serving the sensitive area. He has also successfully excised the scar when a pain complex has arisen following the healing of a wound. To this brief account I ought to

add that only when, as very rarely happens, a sympathetic block fails to give a complete temporary relief should one suspect an hysterical element in the problem. I have seen 1 or 2 patients in whom the edema and cyanosis cleared up in a typical way, but the "numbness" amounted to complete insensibility to pin-prick and was uninfluenced by anything I could do.

It only remains to connect the peripheral diffuse vasospasm of thrombophlebitis and the painful causalgia-like states which sometimes follow it with the post-traumatic painful complexes just described. In the *acute* phase of a femoro-iliac thrombophlebitis, the whole leg, as already related, is painful, pale, edematous and often faintly cyanotic. A sympathetic lumbar paralysis clears up the pain and rapidly diminishes cyanosis and edema. A similar, though less rapid and complete effect, follows separation of the inflamed vein from the structures about it. In the first case, sympathetic block releases the peripheral vasospasm. In the second, the in-going sensory impulses which reflexly excite the sympathetic vasospasm are believed to be modified. In either case, the favorable effect lasts longer than the temporary character of the procedure warrants, as if a vicious reflex, once interrupted, was slow to return.

It is obvious that venous obstruction alone might well and undoubtedly does cause edema and cyanosis. Lymph flow is also reduced. However, such influences are not up for discussion here, but rather a peripheral vasoconstriction capable of being released by sympathetic paralysis (Fig. 3). Ochsner and DeBakey hold that the reflex spasm affects both venules and arterioles, that anoxia of the capillary endothelium occurs, increasing capillary permeability, and so an excess of fluid passes from vessels to tissues whence various factors oppose its removal.

The chronic, painful, postphlebotic states are practically identical with post-traumatic lower-limb causalgias. They have definite earmarks. Pain is excited by long standing or exercise. It varies greatly in character. Edema and cyanosis are always present in some degree. The lower leg is paresthetic. Pin-prick is usually dull, rarely overpainful and pressure on the muscles as by a blood pressure cuff is very unpleasant (Weir Mitchell noticed this tenderness of muscle in some of his causalgias). The arterial oscillations are usually diminished. The essential identity of the postphlebotic with the post-traumatic complex is borne out by their reaction to treatment. Both are dramatically relieved by a sympathetic procaine block. One such block may cure and several injections of procaine at increasing intervals often do so. The postphlebotic complex can be broken up also by interrupting the sensory impulses upon the inflamed vein; the post-traumatic disorder, at the "trigger point," upon the attendant blood-vessels and in the somatic nerve.

The unsolved problem in both the traumatic and phlebotic varieties is, of course, the nature of the pain. Leriche,^{8,9} holds that

the sympathetic supply to the painful part usually modifies and often relieves pain. Sir Thomas Lewis,¹¹ on the other hand, maintains that there are in the skin widely arborizing sensory neurons of a special sort—nocifensors. These have their bodies in the posterior root ganglia. Through axon reflexes in these neurons, alterations occur in the skin and a hypothetical H-substance is formed which

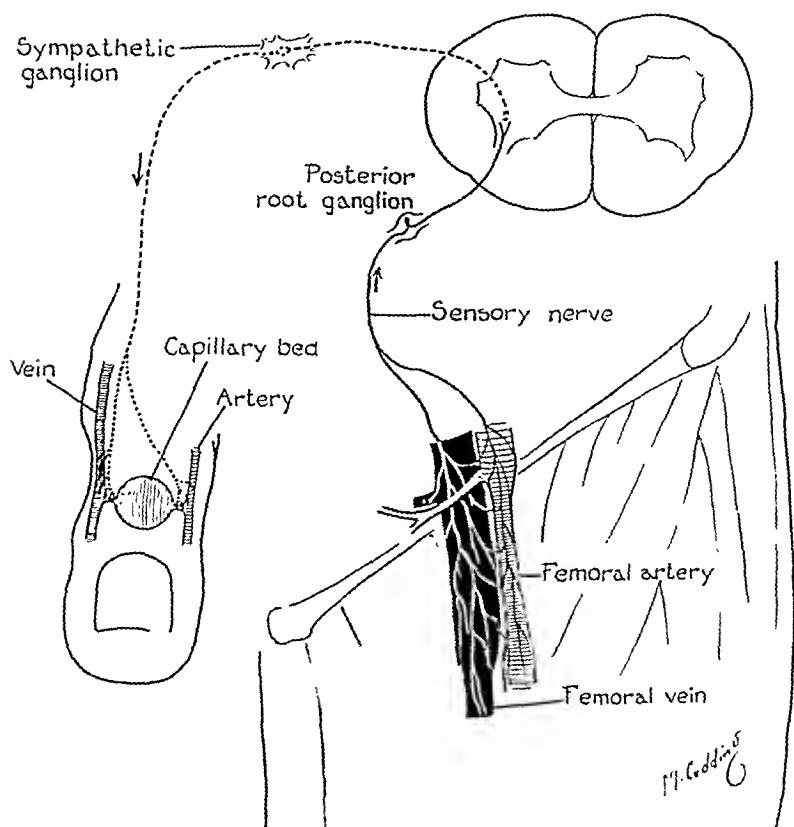


FIG. 3.—From the thrombosed femoral vein irritation is communicated through its sensory filaments, via a somatic nerve and posterior root ganglion, to sympathetic elements in the cord, whence outflowing sympathetic vasoconstricting impulses cause constriction of the arterioles (and venules?) close to the capillary bed in the corresponding extremity. At the same time local constriction of the femoral artery occurs.

reduces the threshold of pain in the sensory nerves. All this takes place, he believes, without the mediation of the sympathetic system. Livingston¹² takes the attitude that sympathetic responses occur in the form of vasospasm in vessels both large and small, as a reaction to a great variety of peripheral injuries; and that sympathetic paralysis profoundly modifies these responses and the pains which go with them—the sort of relief I have been discussing here. He

concludes that: "It seems probable that the injury to certain tissues starts a cumulative process which is not confined to a single nerve distribution and which tends to spread to involve the spinal cord in diffuse reflex phenomena in which the sympathetic nerves are prominently affected."

Comment. I have strayed from my subject of traumatic vasomotor spasm into the difficult question of the pain mechanism, but actually the two problems cannot be separated. In the case of a gross local arterial spasm, pain is necessarily a feature. It appears with the spasm and disappears with its relief. A reflex starting from the irritated vessel and leading, by way of sympathetic neurons, to a widespread spasm of collaterals, is usually evident as a secondary effect leading to a serious ischemia. With the diffuse and milder peripheral vasospasms, such as are seen with and after thrombophlebitis and in post-traumatic states, pain is also prominent. But now its connection with the exciting lesion is less direct and understandable. The sort of injury which excites the pain complex of minor causalgia only exceptionally does so. One must believe that a peculiar progressive and persistent reflex disorder, involving the sensory nerves of the blood-vessels, the spinal cord and the sympathetic system, occasionally and unpredictably is set up. Pain, edema and cyanosis are usually associated. It is hard to see a relationship between these chronic states and the gross vasospasms until it is realized that the irritation of nerves about an inflamed, thrombosed vein can occasion exactly the same local and peripheral vasospasms and pain complexes as are borne of a great variety of injuries. There is yet much to unravel but the interpretation offered here has so far proved useful. Imaginative concepts and painstaking, accurate studies of pathologic physiology should continue to offer solutions for such circulatory puzzles and relieve much suffering and disability.

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SOME OBSERVATIONS ON GASTRITIS AND PEPTIC ULCER*

BY MARY M. MAHER, M.D.†

MAX M. ZINNINGER, M.D.

LEON SCHIFF, M.D.

AND

NATHAN SHAPIRO, M.D.‡

CINCINNATI, OHIO

(From the Departments of Internal Medicine and Surgery of the University of Cincinnati Medical School, and the Gastric Research Laboratory of the Cincinnati General Hospital)

THE literature contains various reports, based on either gastroscopic or histologic studies, of the frequency of gastritis in cases of peptic ulcer. Konjetzny⁶ found gastritis histologically in 100% of his operated patients with peptic ulcer and expressed the belief shared by Faber⁴ that gastritis was a precursor of peptic ulcer. He stated that the gastritis begins in the antrum and later spreads to the body of the stomach. Henning⁵ was also impressed with the regularity of gastritis in patients with peptic ulcer following a study of a large series of resected stomachs. On histologic study Baker¹ found that 90% of gastric ulcers were associated with gastritic changes, particularly in the antral mucosa, and that 60% revealed definite atrophic changes. In about 80% of duodenal ulcers some degree of antral gastritis was present and in 30% the gastritis was of the atrophic type. Templeton and Schindler¹² found gastritis in 37 of 44 patients with gastric ulcer and in 49 of 75 patients with duodenal ulcer examined gastroscopically. The gastritis was most commonly hypertrophic. Atrophic gastritis was found in 4 of the cases of gastric ulcer and in 3 of the group with duodenal ulcer. In a later study Schindler and Arndal¹⁰ found atrophic gastritis in 19 of 79 cases of benign gastric ulcer. In a gastroscopic study of 70 patients with duodenal ulcer Christiansen³ reported the presence of gastritis in 43. Superficial gastritis was found in 34 of the patients, hypertrophic gastritis in 8, and atrophic gastritis in 1.

Our own studies are based on observations in 40 patients with peptic ulcer, 28 of whom had satisfactory gastroscopic examination—

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† Fellow in Gastroenterology in cooperation with the Department of Pathology

‡ Fellow in Gastroenterology; Trainee of the National Cancer Institute.

within 1 month from the time that material was obtained for microscopic examination. Thirty-six of the cases were subjected to partial gastrectomy, and 4 were studied postmortem (following injection of the stomach with formalin immediately after death). Immediately after the resected material was obtained, it was washed with water to remove excess mucus, then gently stuffed with gauze and immersed in formalin. In 23 instances large sections containing part of the lesser and greater curvature of the stomach were obtained as described elsewhere.¹¹ In 10 of the cases material for microscopic examination was obtained within 1 week following the gastroscopic examination, in 10 others within 2 weeks, and in the remaining 8 within less than 4 weeks.

The gastroscopic criteria of the various forms of gastritis used in this study are essentially those of Schindler.⁹ A diagnosis of superficial gastritis was made in the presence of at least two of the following changes: (1) excess of mucus (free of air bubbles), (2) hyperemia (diffuse or patchy), or (3) edema of the folds. Hypertrophic gastritis was diagnosed when any of the following changes were present: (1) verrucous elevations or beading of the rugæ, (2) polygonal areas, or (3) a cobblestone pattern. These changes were usually associated with a velvety appearance of the mucosa and a decrease in highlights. Atrophic gastritis was considered to be present when either grayish areas or branching vessels were visible. These changes were usually associated with improminent or absent rugæ.

The microscopic criteria of atrophic gastritis and its arbitrary gradations of \pm to IV which we have adopted have been given in detail elsewhere.¹¹ The changes consist of varying degrees of (1) infiltration between the glands and ducts with plasma cells and lymphocytes, (2) infiltration between glands and ducts with connective tissue, (3) goblet cell metaplasia, (4) decrease in number of glands, (5) cystic dilatation of glands or gland ducts, (6) lymph follicle hyperplasia and/or increase in number, (7) disappearance of chief and parietal cells, (8) distortion of glands or gland cells, or (9) decrease in width of the mucosa. (All of these changes need not be simultaneously present in a given section.)

We have considered the presence of hyperplasia (increase in the number of glands and in the size of the gland cells) as essential to the *microscopic* diagnosis of hypertrophic gastritis. This type of hyperplasia has been described in detail by Letulle⁷ who pointed out that only to this method of increase in the width of the gastric mucosa can the term hyperplasia be used. Benedict and Mallory² describe the counterpart of the hypertrophic gastritis of the gastroscopist as a chronic gastritis in which there is "exaggeration of the zone of plasma cell infiltration which in some degree is found in almost every stomach." We believe, as Letulle did, that the widening due to infiltration of small round cells, plasma cells and fibrous

tissue, as well as that observed when hyperplasia of lymphoid follicles has ensued, is not a true hyperplasia or hypertrophy. When these processes are associated, as they usually are, with a decrease in the glandular elements of the mucosa, atrophic gastritis is present.

At the present time we do not consider any particular microscopic change as characteristic of superficial gastritis. On the basis of biopsy studies Schindler⁸ believes that the superficial gastritis seen by the gastroscopist consists of edema and plasma cell infiltration of the connective tissue stalk between the gland duct openings and mucin distention of the cells above the neck cell zone, including the surface epithelium with flattening, to a basilar position, of the nuclei of these cells. Benedict and Mallory² have described superficial gastritis as an acute exudative process in which mucin vacuoles grow smaller and disappear from the cells above the neck cell glands, which they normally completely fill, and in which polymorphonuclear leukocytes appear in large numbers in the interstitial tissues of the upper portions of the mucosa.

In comparing the gastroscopic and microscopic findings of gastritis in cases of peptic ulcer, there are certain difficulties. The antrum which may be the seat of the most marked gastritis in cases of peptic ulcer may be poorly visualized gastroscopically. The time elapsing between the gastroscopic examination and resection or autopsy may permit the appearance or disappearance of mucosal changes. The degree of gastritic change in the so-called normal stomach needs yet to be determined. Finally, there are certain portions of the stomach which are not seen during gastroscopy. These include the lesser curvature of the antrum, part of the greater curvature along which the instrument passes, part of the posterior wall, and part of the fundus.

It will be seen from Table 1, which lists the gastroscopic findings in 28 of the cases in which a satisfactory gastroscopy was carried out, that the stomach appeared normal in 12 instances. In 10 cases superficial gastritis was present; in 5, hypertrophic gastritis was found; and in 1, there was a combination of superficial and hypertrophic gastritis. In no instance were definite atrophic changes found.

TABLE 1.—GASTROSCOPIC FINDINGS IN 28 CASES OF PEPTIC ULCER

Gastro-copic diagnosis*	No. cases of gastric ulcer	No. cases of duodenal ulcer	Total
Normal stomach	6	6	12
Superficial gastritis	4	6	10
Hypertrophic gastritis	3	2	5
Superficial and hypertrophic gastritis	1	0	1
Total	14	14	28

* This pertains only to mucosal changes exclusive of the presence of ulcer.

Table 2 depicts the microscopic changes in the gastric mucosa in the 40 patients studied. Most striking is the presence of an atrophic gastritis of Grade II to Grade IV in 35 of the cases. Evidence of



FIG. 1.—C. S. 56-w-m. Duodenal ulcer. Cystic dilatation of the glands is a prominent feature of the atrophic gastritis in this stomach. ($\times 160$.)



FIG. 2.—A. K. 48-w-m. Gastric ulcer. Goblet cell metaplasia is found frequently in this stomach with far-advanced atrophic gastritis. ($\times 160$.)

hyperplasia was seen in 16 cases and was always associated with atrophic gastritis. Photomicrographs from 2 of the cases are shown in Figures 1 and 2 emphasizing particularly the atrophic changes.

TABLE 2.—MICROSCOPIC CHANGES IN GASTRIC MUCOSA OF 40 CASES OF PEPTIC ULCER

Microscopic diagnosis	No. cases of gastric ulcer	No. cases of duodenal ulcer	Total
Normal mucosa*	2	2	4
Atrophic gastritis, Grade I	0	1	1
Atrophic gastritis, Grade II to IV	14	21	35
<hr/>			
Hyperplasia†	4	12	16
Polyps†	0	2	2

* This includes 3 cases of atrophic gastritis, Grade \pm considered normal.

† These changes are additional to the atrophic gastritis listed above the broken line.

TABLE 3.—CORRELATION OF GASTROSCOPIC AND HISTOLOGIC DIAGNOSIS OF GASTRITIS IN 28 CASES OF PEPTIC ULCER

Gastroscopic diagnosis*	No. of cases	Microscopic findings			
		Normal mucosa†	Atrophic gastritis (I-IV)	Hyperplasia	Atrophic gastritis and hyperplasia
Normal mucosa	12	—	8	—	4
Hypertrophic gastritis	5	—	2	—	3
Superficial gastritis	10	3	3	—	4
Superficial and hypertrophic gastritis	1	—	1	—	—

* This pertains only to mucosal changes exclusive of the presence of ulcer.

† Atrophic gastritis, Grade \pm , considered normal.

Table III emphasizes the rather startling discrepancy between the gastroscopic and microscopic diagnoses in these cases. In 12 instances in which the stomach appeared normal at gastroscopy, definite gastritic changes were present in all, the changes being a combination of atrophic gastritis and hyperplasia in 4, and atrophic gastritis in 8. In 10 patients in whom a gastroscopic diagnosis of superficial gastritis was made, 4 showed atrophic gastritis and hyperplasia, 3 showed atrophic gastritis, and 3 showed either a normal stomach or a \pm atrophic gastritis which we consider within normal limits. In none of the 10 cases of superficial gastritis, 9 of which were examined within 11 days of resection, did we find evidence of an acute exudative process such as that described by Benedict and Mallory in 25 of 33 of their cases with a gastroscopic diagnosis of superficial gastritis. Edema, hemorrhage, plasma cell infiltration and mucin distention of the cells above the neck cell zone with flattening to a basilar portion of the nuclei of these cells, as described by Schindler, were no more prominent in the cases with superficial gastritis than in the other cases.

Of much interest is the fact that the atrophic gastritis which we reported to be present microscopically in 28 of 35 cases of gastric

cancer¹¹ was largely similar to that described in the group of ulcer patients here reported except for the association of hyperplasia in 16 instances of the ulcer group. This is contrary to what one would expect from the difference in the gastroscopic appearances in the two groups of patients.

Summary. Atrophic gastritis of an arbitrary Grade I to IV was found microscopically in 36 of 40 proved cases of peptic ulcer. The gastritis did not vary essentially from that previously reported in a group of 35 cases of gastric cancer except that evidence of hyperplasia was found in 16 cases.

The gastric mucosa appeared normal in 12 cases, superficial gastritis was present in 10, and either hypertrophic gastritis or hypertrophic and superficial gastritis was present in 6 of 28 patients who had satisfactory gastroscopic examinations within 1 month of resection or autopsy. Microscopically, atrophic gastritis was found in all of the 12 cases which were normal at gastroscopy and in 13 of the remaining 16. This discrepancy may be explained in part by the presence microscopically of a certain degree of atrophic gastritis in the so-called normal stomach and by the masking of atrophic changes by superficial or hypertrophic gastritis.

The fact that the gastritis associated with peptic ulcer is largely similar to that seen in patients with gastric cancer strongly suggests that the gastritis *per se* may not be a *specific* precursor of either gastric cancer or peptic ulcer.

The frequent presence of microscopic evidence of atrophic gastritis in a stomach which appears normal gastroscopically indicates the necessity for further study of control groups of stomachs.

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LATE POSTOPERATIVE FOLLOW-UP STUDIES ON PATIENTS WITH RECURRENT APPENDICITIS

By GEORGE J. WILLAUER, M.D.

ASSOCIATE IN SURGERY, JEFFERSON MEDICAL COLLEGE HOSPITAL
PHILADELPHIA, PA.

AND

JAMES F. O'NEILL, M.D.*

RESIDENT IN SURGERY, BOWMAN GRAY SCHOOL OF MEDICINE, WAKE FOREST COLLEGE
WINSTON-SALEM, N. C.

(From the B Surgical Service, Jefferson Medical College Hospital)

ALMOST all authorities on the subject of right lower quadrant pain express warnings to be cautious and thorough in diagnosis and treatment, and advise healthy skepticism in condemning the appendix and advising its removal. Experiences in the surgical follow-up clinic certainly corroborate the opinions found in the literature.

The physician must be cognizant of the many sites of origin which right lower quadrant pain may have, for it may spring from various intestinal, renal, genital, thoracic lesions or have orthopedic and functional sources.^{1,2} The relative frequency with which the pain arises from any of these causes is not known since the statistics of an individual writer will be altered by the specialty in which he is engaged.

It is common experience that careful study of a patient may fail to disclose any positive cause for lower abdominal or right lower quadrant pain; the diagnosis, therefore, being made by exclusion, and removal of the appendix advised.

If laparotomy is carried out, a gross pathologic lesion may or may not be found to account for the patient's symptoms; instead, minor degrees of abnormality either in the appendix or in some other organ may be encountered and interpreted according to the individual opinions of the operator. There are certainly not a few cases in which the abdominal viscera appear normal, and here again, the description of the operative findings is colored by the thoughts (sometimes wishful) of the surgeon.

Method. In order to study the efficiency of the diagnostic and therapeutic measures employed on patients suffering with right lower quadrant pain, and treated in the wards of the B Surgical Service of Jefferson Medical College Hospital, the histories and follow-up records of 375 cases were reviewed through the Surgical Follow-Up Clinic. In most instances, these patients were diagnosed preoperatively as subacute or chronic appendicitis and were operated on between May, 1929, and July, 1940. The period of

* This work was done while Ross V. Patterson Fellow in Surgery, Jefferson Medical College Hospital.

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postoperative observation varied from 3 months to 11 years (average, 22.9 months). Eight patients with similar diagnosis, but in whom procedures other than the removal of the appendix were performed, are not included in this follow-up study.

The diagnosis of the pathologist was tabulated in all instances in which it could be obtained. The presence of inflammatory reaction and fecaliths was not tabulated unless mentioned in the pathologist's report.

The various types of histologic diagnosis, and their relative frequency are tabulated in Table 1. Out of the 375 cases, a laboratory record of the removed tissue was available in 255.

TABLE 1.—PATHOLOGIC DIAGNOSIS

Appendix without microscopic lesion	104
Lymphoid hyperplasia	75
Chronic appendicitis	32
Acute appendicitis	21
Hemorrhage and necrosis in mucosa	8
Fecalith in lumen	8
Fibrosis	5
Subacute appendicitis	1
Oxyuris vermicularis	1
Total . . .	255

Pathologically, the largest group, 104 cases, was made up of appendices which showed no evidence of organic disease. In 75 cases, lymphoid hyperplasia was noted and varied in degree from slight to marked. In 32 cases, chronic appendicitis was diagnosed histologically, while in 21 cases, acute appendicitis was found.

The majority of the patients in this series were between the ages of 10 and 39; the greatest incidence, 42.4% being in the second decade of life (Table 2).

TABLE 2.—AGE INCIDENCE

	No.	%
1 to 9 years	17	4 5
10 to 19 "	159	42 4
20 to 29 "	131	34 9
30 to 39 "	46	12 3
40 to 49 "	18	4 8
50 to 59 "	4	1 0

There were 231 females and 144 males, a ratio of 1.6 to 1. These figures vary somewhat from those given by Zisserman⁶ who, in reviewing 391 cases of chronic appendicitis, reported 287 females and 104 males, a ratio of 2.7 to 1. The average age for patients in his series was 22.4 years.

In 48.4% of the patients, symptoms had been present at intervals for 6 months or more (Table 3) while only 4% of the total number gave no history of any attacks of pain prior to their present illness. It is interesting to note that of the 15 patients who were operated

on following their first attack, 14 were symptom-free postoperatively and 1 had occasional pain in the region of the scar.

TABLE 3.—HISTORY OF ATTACKS

	No.	%
2 years and over	91	24.2
1 to 2 years	31	8.0
6 months to 1 year	61	16.2
Less than 6 months	110	29.4
No previous attack	15	4.0
Not noted	67	17.8

Pain was the chief symptom in all except 1 patient, and was present in the right lower quadrant only in slightly more than half of the cases (51.7%) (Table 4).

TABLE 4.—LOCATION OF PAIN

	No.	%
Right lower quadrant	194	51.7
Generalized, localizing in R.L.Q.	35	9.4
Epigastric, radiating to R.L.Q.	28	7.4
Umbilical radiating to R.L.Q.	18	4.7
R.L.Q. radiating to loin or back	18	4.7
R.L.Q. radiating to L.L.Q.	16	4.2
Epigastric	13	3.4
R.L.Q. radiating to right thigh	11	2.9
Peri-umbilical or generalized	10	2.6
R.L.Q. radiating to R.U.Q.	8	2.1
Hypogastric	3	0.8
R.U.Q. radiating to loin	2	0.5
"All over abdomen"	1	0.3
No pain	1	0.3
Not noted	17	4.5

Other types of pain, varying in location and radiation, made up the rest of the group. The patient who had no pain, a 23-year-old male, complained of nausea and abdominal distention for 2 years prior to admission. At operation, his appendix was found to be hard, elongated and slightly injected. However, following appendectomy, he has been symptom-free.

Nausea was present in about one-third (32.2%) of the cases; vomiting alone in 8.5% and nausea with vomiting in 24.1% of the cases.

The leukocyte counts were within normal limits in the majority of cases. This was probably due to the mild or moderate degree of the illness, plus the fact that many leukocyte counts were made during the so-called "interval" period between attacks of pain. Of the leukocyte counts made, 68.3% were between 5000 and 10,000 per c.mm.; 5.1% were below this figure, 16.6% were above it, and in 9.6% of the cases, no records of leukocyte determinations were found.

Operative descriptions indicated that some appendices were normal, some were kinked or were fixed by adhesions or congenital bands, and were said to show various grades of inflammatory reac-

tion or serosal injection. Speaking from the gross pathologic aspect, evidences of inflammation were described in 105 cases from that group having a pathologic report. Yet, if the laboratory findings were reviewed and the chronic, subacute and acute appendices totaled, there were only 54 cases in which the pathologist corroborated the clinical opinion.

There were 49 cases in which fecaliths were reported in the operative notes (Table 5). Forty-three of these patients had no pain postoperatively and the remaining 6, with postoperative symptoms, had had recurrent attacks of right lower quadrant pain accompanied by nausea and vomiting before admission to the hospital. The duration of onset varied from 8 days to 1½ years before operation, at which time nothing but the removal of the appendix was performed. Of the 6 with postoperative symptoms, 1 woman had pain only after walking rapidly. Four (2 men and 2 women) had pain only when constipated. The third man had occasional return of his preoperative pain, which he cannot associate with any activity or function. He has a history of a loss of 20 pounds in weight and diarrhea but no note has been made as to any investigation of these symptoms. In this group having the lumen of the appendix obstructed by fecaliths, 87.8% were symptom-free after operation. Four of the 6 patients with right lower quadrant pain postoperatively accompanied by constipation no doubt have symptoms because of increased pressure in the cecum as a result of a spastic colon and a competent ileocecal valve.

TABLE 5.—INTRALUMINAL OBSTRUCTION

Findings	Symptom-free	Pain following appendectomy
Fecaliths	43	6
Oxyuris vermicularis	1	—
Total	44	6
Percentage	88	12

In 27 patients the appendix was found to be in the retrocecal position.

Clinically, 21 patients were felt to have normal appendices, whereas histologically it was reported 104 times. Obstructive phenomena, due either to malposition or kinking, or containing fecaliths, noted clinically and absent pathologically, will account for many of the apparent discrepancies between the clinical and pathologic diagnosis. Wangenstein⁴ had demonstrated that an increase in intraluminal pressure of an otherwise normal appendix causes pain.

In 9 cases, enlarged mesenteric nodes were reported, but in only 2 instances in this series was diagnosis of mesenteric adenitis made before operation. All 9 patients were symptom-free postoperatively. Histologic examination of the group showed 3 appendices with

lymphoid hyperplasia, 2 normal and 1 with signs of chronic inflammation. In 3 cases no pathologic report was secured.

Pathologic changes were noted in abdominal viscera other than the appendix in 32 patients; 29 females and 3 males. Table 6 shows the pathologic changes in these organs and the symptomatic results obtained by operation. Out of this group, 25 patients (78%) were symptom-free postoperatively; 1 patient (3.1%) had a definite recurrence of her preoperative pain, and 6 patients (18.7%) complained of some abdominal discomfort, difficult to evaluate, yet sufficient to prevent their classification among the group cured.

TABLE 6.—PATHOLOGIC CHANGES IN OTHER ORGANS

Pathologic changes noted	Sex	Follow-up
Retroverted uterus	F	Occ. pain in R.L.Q.
	F	Same pain; worse at menses
Cyst of right tube	F	Symptom-free
Simple cyst of right ovary	F	"
	F	"
	F	"
	F	Occ. R.L.Q. pain
	F	Occ. R.L.Q. pain
Adherent right ovary	F	Symptom-free
	F	"
Redundant colon	F	Soreness in R.L.Q.
	F	Pain in L.L.Q.
	F	Symptom-free
Adhesions between gall bladder and stomach	M	"
Ptotic kidney, right	F	"
	F	"
	F	"
Distended gall bladder	M	"
Peritonitis	M	"
Fluid in pelvis	F	"
Injected ileum	F	Painful scar
	F	Symptom-free
Enlarged right lobe of liver	F	"
Mesenteric adenitis	F	"
	F	"
	F	"
	F	"
	F	"
	F	"
	F	"
	F	"

Results. The symptomatic results observed, interpreted and tabulated in the Follow-Up Clinic are given in Table 7. There were no deaths. Two hundred and sixty-four patients (70.4%) were free of pain and are classified as cured. The symptoms presented by the remaining patients were sometimes difficult to diagnose. It was impossible to determine whether their postoperative symptoms were partly or entirely the same as their preoperative ones, or whether they had developed new complaints since leaving the hospital. Eighty-four patients had postoperative pain differing

in nature from their preoperative symptoms. All had some degree of abdominal discomfort varying in location, radiation, and frequency of occurrence, and were difficult to classify because of the wide range of variability. They are regarded as unsatisfactory results and will require further observation to determine whether their postoperative complaints are related to, or independent of, their preoperative symptoms. One patient, a 37-year-old male whose preoperative diagnosis was appendicitis and who was operated on in May 1933, was readmitted in 1934, 1935 and again in 1939 because of hemorrhage from a duodenal ulcer. He refused surgery until his fourth hemorrhage in April, 1941, when a subtotal gastrectomy was done. Undoubtedly, his original difficulties were due to a duodenal ulcer, unrecognized because of atypical symptoms.

TABLE 7.—SYMPTOMATIC RESULTS REFERRING TO PAIN

Pathologic diagnosis	No pain	Same pain	Pain-ful scar	Pain on effort	Pain in RLQ, LLQ	Abd. pain	Hypo-gastrie pain	RUQ pain	Ulcer	Not noted
Appendix without microscopic lesion	75	10	3	2	10	3	..	1		
Chronic	24	2	3	1	.	2				
Subacute	1									
Acute	18	..	1	..	2					
Lymphoid hyperplasia	52	1	3	1	12	6				
Fecaliths	5	1		.	1					
Hem. or necrosis in mucosa	4	2		.	2					
Fibrosis	2			1	2					
Oxyuris vermicularis	1					
No pathologic report	83	11	3	.	17	1	2	2	1	1
Totals	264	27	13	5	47	12	2	3	1	1
Percentage	70.4	7.5	3.5	1.3	12.5	3.2	.5	.7	.2	.2

It was definitely thought that 27 patients had exactly the same pain postoperatively as they had complained of preoperatively. In this group were 19 females and 8 males. Their appendices were classified pathologically as follows: normal, 10; hemorrhage in mucosa, 2; chronic inflammation, 2; lymphoid hyperplasia, 1; fecaliths, 1; no pathologic report, 11.

Eight patients in this group suffered from moderate to severe dysmenorrhea, associated with menstrual irregularity. Two of the patients were thought by the psychiatrists to have mental retardation and psychoneurosis, while 4 others, who were not definitely diagnosed as neurotics, might well be classified among this group, judging from their chronic and bizarre symptomatology, the organic origin of which was never demonstrated by thorough study.

A 43-year-old man, unimproved following appendectomy, has Roentgen ray evidence of right sacro-iliac arthritis. His appendix had shown lymphoid hyperplasia. A 22-year-old woman had a fractured pelvis 2 years prior to admission. When first allowed to walk following her injury she had pain in her right lower quadrant. She then began to have attacks of right lower quadrant pain accompanied by nausea and vomiting and aggravated during her menstrual periods. She had tenderness in her right lower quadrant

extending around to her right flank. Roentgen ray examination of her bones showed a normal pelvis but an old injury to the transverse process of her fifth lumbar vertebra. Appendectomy was done, and at operation the patient was found to have a bleeding left ovarian cyst. Following operation she had a recurrence of the pain in her right lower quadrant. It was difficult to determine whether the patient's symptoms were due to ovarian dysfunction or the referred pain as a result of her old injury.

Good follow-up records concerning the condition of the operative scars were secured in all but 82 cases (Table 8). The vast majority, 255, were painless and well-healed. Two patients had weak scars with evidence of partial separation of the fascia, but no definite hernia. Four patients complained of some "bulging" or a transient "lump" in their incision. In only 1 of these was there a vague sensation of an impulse on straining. No definite hernias were found.

TABLE 8.—CONDITION OF SCARS

	No.	%
Painless and well healed	255	68.0
"Weak"	2	0.5
Hernia (?)	4	1.0
Scar occasionally painful	14	3.7
Scar painful on exertion	4	1.0
Scar painful in damp weather	2	0.5
Keloid formation	12	3.2
Not noted	82	22.1
Total percentage	—	100.00

Twelve cases of keloid formation were presented. No wound infections were reported, however.

Discussion. Analysis of our follow-up records of 375 cases of appendicitis, almost all of which were recurrent, indicates that our experiences agree closely with those reported from other clinics. The percentages of cures, following appendectomy, reported by various authors vary between 74% and 87%. Of our 375 cases, 264 (70.4%) were completely cured of any preoperative symptoms following appendectomy, and a total of 348 (92.8%) were either completely or partially relieved of pain. The remaining 27 patients (7.2%) had exactly the same postoperative pain as they had preoperatively. In a recent article on this subject, Warren and Ballantine³ report that, following operation, three-fourths of their patients with recurrent right lower quadrant pain were either completely or partially relieved.

The opinion of the pathologist concerning the appendix may or may not be significant; but every organ removed should certainly be submitted for laboratory examination. It is to be expected that many appendices demonstrating adhesions, kinks or congenital bands will show no internal micro-copic pathologic change. As the pathologist is not in as good a position as the surgeon to evaluate the

significance of such instances, it seems justifiable to adhere to the surgical description, and to regard the pathologist's report as of minor importance in formulating the final diagnosis. When, however, the pathologist corroborates the clinical description of an inflamed but otherwise normal appendix in only 54 out of 166 instances, a serious discrepancy exists. As the histologic diagnosis of inflammation is unquestionably the more objective, it should be taken as the standard. Most of the difficulty is really the result of inadequate terminology, as is often the case in medical disagreements. It is inaccurate to diagnose mechanical appendiceal lesions as inflammatory—an error that surgeons commit each time they make a diagnosis of chronic appendicitis. Until more accurate nomenclature is adopted, the term "recurrent" is probably the least incorrect, and is to be preferred to the adjective "chronic."

The group of 27 patients who had a recurrence of their preoperative pain, as well as the patients who had various other postoperative pain, are admittedly difficult to classify. As a group, there are certain features which stand out. Two-thirds of these individuals are women with a definite history of irregular menstruation and dysmenorrhea, suggesting endocrine dysfunction. Some are constipated or complain of anorexia, belching, bloating and indigestion. Three were described as very poorly nourished. This presents the problem of dietary deficiencies, particularly referring to the insufficient intake of the B complex. Since this factor is known to have a specific relation to gastro-intestinal motility, the lack of an adequate intake of it may give rise to signs and symptoms mimicking appendiceal or gall bladder disease.³

Four of these patients, we now believe, are neurasthenics, and while caution must be exercised in making such a diagnosis, it should, when proper evidence is at hand, be made, and appendectomy not advised.

Regular periods of observation in the follow-up clinic is the only accurate method of determining the status of a group of patients presenting a varied symptomatology and who were clinically diagnosed as appendicitis.

Conclusions. An accurate observation of the patient and a study of his symptoms are necessary before advising appendectomy. Three hundred and twenty-four of our patients were hospitalized 12 days or longer, giving the ward surgeon 2 to 4 days to observe the case. Thirty-five others were hospitalized from 21 to 37 days. On all of these patients hospitalized longer than the average case of appendicitis, we made special studies such as urograms, serial examination of catheterized urine, and gastro-intestinal Roentgen ray examinations, particularly the barium enema. We reviewed the studies recorded on the histories but were unable to discover the discrepancies between the clinical and pathologic diagnosis.

We urge that nutritional deficiencies be given greater consideration in the group of patients diagnosed clinically as having recurrent appendicitis.

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THE ABSORPTION, EXCRETION AND TOXICITY OF PENICILLIN ADMINISTERED BY INTRATHECAL INJECTION*

BY CHARLES H. RAMMELKAMP, M.D.

AND

CHESTER S. KEEFER, M.D.

BOSTON, MASS.

(From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine)

In view of the fact that certain types of meningitis fail to respond satisfactorily to therapy with the sulfonamide drugs, a study was undertaken to determine the effectiveness of penicillin treatment in staphylococcal and pneumococcal meningitis. As a part of this investigation the absorption, excretion and toxicity of penicillin following intrathecal injection were studied.

Materials and Method. In all, 6 subjects received intrathecal injections of penicillin. They included 1 patient with idiopathic epilepsy, 1 with rheumatoid arthritis, 2 with meningitis and 2 with brain abscess and meningitis. During the period of study the fluid intake was not limited.

An 0.85% solution of sodium chloride containing 1000 Florey units of the sodium salt of penicillin† per cubic centimeter was used in each subject. This solution was stored at 5° C. until the time of injection.

After the removal of at least 10 cc. of spinal fluid, penicillin, varying from 3000 to 10,000 Florey units, was injected intrathecally. For as long as 7 hours after the penicillin had been administered numerous samples of blood were withdrawn from the antecubital vein. The blood was placed in sterile tubes and allowed to clot, following which the serum was separated by centrifugalization.

Repeated lumbar punctures were performed subsequent to the injection. After the intrathecal pressure had been measured 1 to 10 cc. of fluid was removed and the number of cells per cubic millimeter recorded. In addition, in 2 subjects fluid was obtained at time of autopsy from the ventricular system.

In several subjects all urine was collected for a period of 24 to 48 hours. These specimens were obtained in sterile containers from males and by catheterization from females. The samples of blood serum, spinal fluid and

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† We are indebted to Dr. George A. Harrop, the Squibb Institute for Medical Research, New Brunswick, N. J., for a liberal supply of penicillin.

urine were stored at 5° C. until the time of testing. If a sample was known to be contaminated, it was passed through a Seitz filter to effect sterilization.

The method used to determine the concentration of penicillin in body fluids has been described in detail elsewhere.⁶ Briefly, it consists of making 3 to 14 serial dilutions of 0.2 cc. of the unknown sample. As a control, a standard solution of penicillin containing 4 Florey units per 0.2 cc. is diluted in a similar manner. To the various dilutions of the control and unknown samples is then added 0.5 cc. of veal infusion broth containing 1% erythrocytes and 1000 to 10,000 hemolytic streptococci. All tubes are incubated for 18 to 24 hours and then examined for growth. Repeated tests have demonstrated that the smallest amount of penicillin required to sterilize the culture is 0.0039 Florey unit. By observing the greatest dilution of the unknown sample in which all streptococci are killed, it is possible to determine the concentration of penicillin in the sample.*

RESULTS OF INTRATHECAL ADMINISTRATION OF PENICILLIN
IN A NORMAL INDIVIDUAL

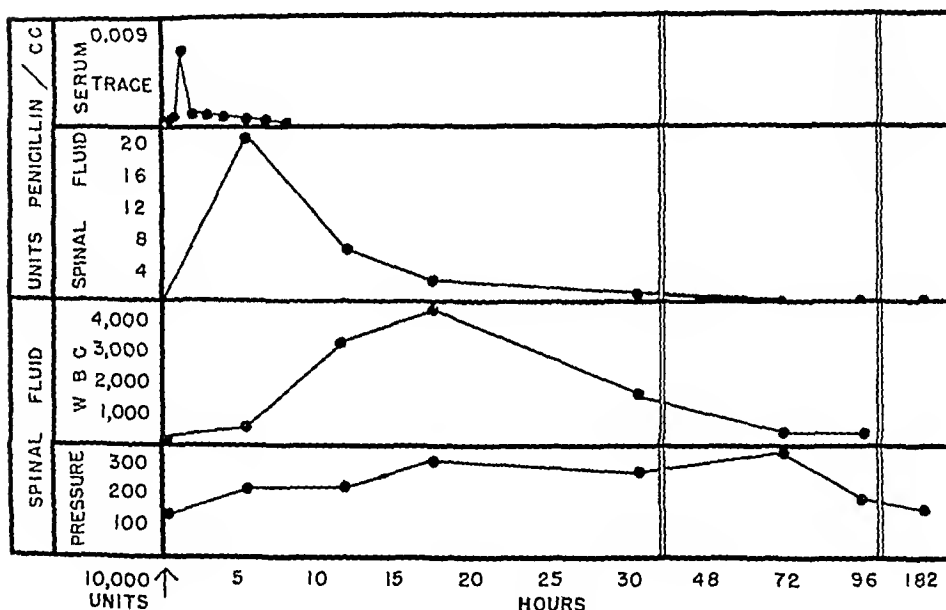


FIG. 1.—Results of intrathecal administration of penicillin in a normal individual.

Results. *Absorption, Excretion and Toxicity in Subjects Without Brain Abscess or Meningitis.* Figure 1 shows the essential observations made on Subject 1, a male 17 years of age with idiopathic epilepsy, after the intrathecal injection of 10,000 Florey units of penicillin. With the exception of one sample of blood obtained 70 minutes after the injection, the serum contained no appreciable amount of penicillin. Six hours following the injection the spinal fluid contained 25 Florey units per cc. The level then fell rather rapidly so that at 31.5 hours there was only 0.078 Florey unit per cc. and at 72 hours no trace of penicillin remained.

* All figures recorded in this paper on the concentration of penicillin in body fluids are subject to the errors of dilution methods in general.

Not included in Figure 1 is the excretion of penicillin in the urine. There was apparently a suppression of urine formation in this subject since the first specimen of 30 cc. was passed 18 hours after the injection. This sample contained 75 Florey units. The total volume of urine in the first 37 hours of observation was 819 cc. and the total number of Florey units of penicillin excreted was 997. The total excretion amounted, then, to about 10% of the administered dose.

The intrathecal injection of 10,000 Florey units resulted in a great increase in the number of cells in the spinal fluid. At 6 hours the leukocytes numbered 570 and at 18 hours reached a peak of 4170 per c.mm. The number of cells gradually decreased so that at 96 hours a total of only 250 leukocytes was recorded. Of some interest is the fact that all cells were actively motile. Concomitant with the cellular response in the spinal fluid, the number of leukocytes in the blood increased from 7250 to a maximum of 18,600, 29 hours after the injection of penicillin.

Within 45 minutes after the injection the subject complained of a severe headache. This complaint was relieved by 0.06 gm. of codeine sulfate. At 4 hours the headache recurred and was associated with vomiting. A lumbar puncture performed 6 hours after the injection showed that the pressure had increased from 130 to 210 mm. of water. The headache was only partially relieved when the pressure was reduced by the removal of several cubic centimeters of spinal fluid. The headache and vomiting continued for the first 24 hours and thereafter gradually diminished. There was no rigidity of the neck or elevation of temperature during this period.

Subject 2, a male 28 years of age with rheumatoid arthritis, received 5000 Florey units of penicillin intrathecally. No toxic symptoms followed the injection other than a mild headache which lasted only 30 minutes. Blood samples obtained at frequent intervals during the first 4 hours of observation failed to show any penicillin in the serum. As is shown in Figure 2, the spinal fluid contained 31.2 Florey units per cc. 8 hours after the injection. At 26 hours the concentration had dropped to 0.625 Florey unit and at 44 hours all traces of penicillin had disappeared.

In this subject the maximum leukocyte response recorded in the spinal fluid was 740 per c.mm. at 26 hours after the injection. The number of leukocytes fell rapidly and at 98 hours only 50 cells per c.mm. remained. The spinal fluid pressure was not elevated above a normal level during the period of observation.

The excretion of penicillin in the urine was delayed; however, a total of 1121 Florey units was found in the urine during the first 24 hours.

Absorption and Excretion in Subjects With Meningitis. Subject 3, a female aged 23 years with military tuberculosis and tuberculous meningitis, received an intrathecal injection of 10,000 Florey units.

Figure 3 shows the results obtained. It will be noted that 0.078 Florey unit per cc. of serum was found in the first sample of blood

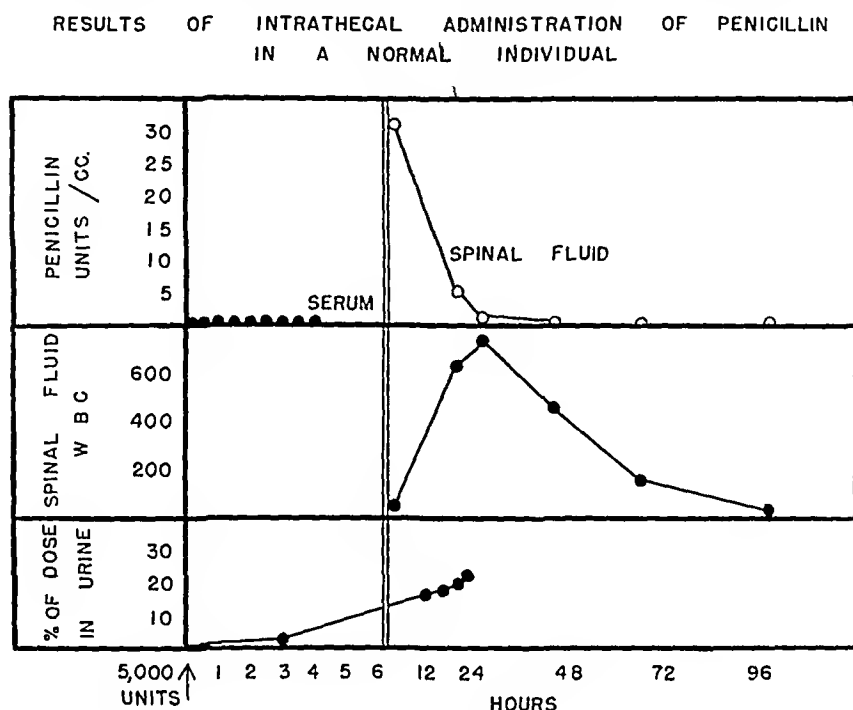


Fig. 2.—Results of intrathecal administration of penicillin in a normal individual.

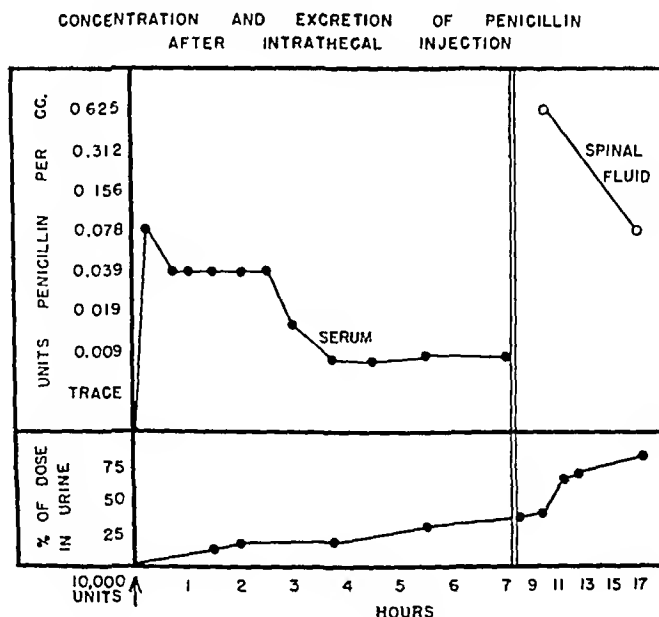


Fig. 3.—Concentration and excretion of penicillin after intrathecal injection.

taken 15 minutes after the injection. Thereafter, all samples of serum obtained at intervals up to 7 hours continued to show a significant level of penicillin.

The level of penicillin in the spinal fluid decreased rapidly, as shown by the low concentration of 0.625 Florey unit per cc. of fluid in the 10-hour sample. At 17 hours the spinal fluid contained only 0.078 Florey unit.

Before penicillin was injected the intrathecal pressure was 300 mm. of water and 10 hours later it was 500. At 17 hours after the injection the pressure had fallen to 320. At no time during the period of observation were there any untoward symptoms.

The total volume of urine passed during the collection period of 17 hours and 30 minutes was 478 cc. This urine contained 7848 Florey units (78% of the administered dose).

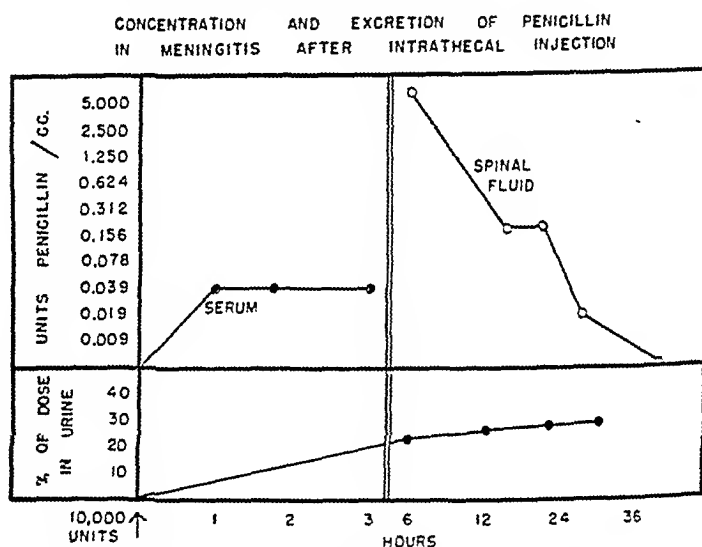


FIG. 4.—Concentration and excretion of penicillin in meningitis after intrathecal injection.

Subject 4, a 5-month-old female infant with Type VIII pneumococcal meningitis, was given 3000 Florey units intrathecally. In addition, this patient received an intravenous injection of 2000 Florey units every 4 hours. No blood or urine samples were studied. The spinal fluid obtained just prior to the intrathecal injection contained 1700 leukocytes per c.mm. Twenty-four hours later the fluid contained 6400 leukocytes and 0.625 Florey unit of penicillin per cc. A second intrathecal injection was given and 9 hours later the infant died. Fluid obtained at time of autopsy from both the spinal canal and the cisterna magna contained 2.5 Florey units per cc. The heart's blood contained 0.625 Florey unit per cc. of serum.

Absorption and Excretion in Subjects With Brain Abscess and Meningitis. Figure 4 shows the absorption and excretion of peni-

cillin in Subject 5, who received an intrathecal injection of 10,000 Florey units. This patient, a 34-year-old woman, developed a brain abscess and meningitis secondary to chronic empyema. Following the intrathecal injection, penicillin was absorbed so that the samples of blood taken 1, 2 and 3 hours later contained 0.039 Florey unit per cc. of serum.

The leukocyte count prior to penicillin administration was 15,624, and 12 hours after it was 51,000 per c.mm. of spinal fluid. The count then fell rapidly, so that at 21 hours the fluid contained 11,980 cells per c.mm.

The subject excreted penicillin over a period of 28 hours, the largest amount being excreted in the first 6 hours. The sample obtained 6 hours after the injection contained 2310 Florey units, which was 23% of the administered dose. In all, only 2727 Florey units were excreted in the urine.

Spinal fluid obtained by lumbar puncture 6 hours after the intrathecal injection contained 5 Florey units per cc. At 27 hours the concentration had fallen to 0.019 Florey unit, and at 40 hours no penicillin remained.

Sixty hours after the first intrathecal injection, a second dose of 5000 Florey units was given. Two and a half hours later the spinal fluid contained 10 Florey units per cc. The patient died 5 hours after the second injection, and fluid obtained from the third ventricle at postmortem was found to contain 0.039 Florey unit.

Subject 6, a 42-year-old man with a diagnosis of brain abscess, meningitis and chronic empyema, was given an initial intrathecal injection of 10,000 Florey units. No studies were made on the blood concentrations or the urinary excretion, since in addition to the intrathecal injections the patient received 35,000 Florey units subcutaneously. The initial leukocyte count in the spinal fluid was 1260 per c.mm. At the time of the second lumbar puncture 24 hours later it was 4600, and the fluid contained 1.25 Florey units per cc.

An injection of 5000 Florey units was made at the time of the second lumbar puncture, and 24 hours later the fluid contained 0.039 Florey units per cc. and the cells numbered 4600. Forty-eight hours after this injection there was no penicillin in the spinal fluid and the leukocyte count was 1530.

A third and fourth injection of 5000 Florey units each were made, and 24 hours after each injection the spinal fluid contained no penicillin. The leukocyte count 7 days after the initial injection of 10,000 Florey units was 136. At no time did the patient display toxic symptoms during the penicillin administration.

Discussion. It has been demonstrated that penicillin does not pass through the blood-brain barrier in significant quantities following an intravenous injection of the substance.⁷ However, absorption of penicillin was observed when injected into closed cavities.⁷ In general, it was found that the absorption and excretion of peni-

cillin injected into the body cavities were likely to be delayed. In 1 subject the chest fluid aspirated 22 hours after the local injection of 10,000 Florey units showed a concentration of 0.78 Florey unit per cc.⁷

The above observations, together with the fact that penicillin is relatively non-toxic for tissues in general, led to the study of the absorption and excretion of the substance after intrathecal injection.

In a subject (No. 1) with idiopathic epilepsy, little penicillin was found in the blood serum following the intrathecal injection of 5000 to 10,000 Florey units. After the injection of 10,000 units the spinal fluid obtained 31.5 hours later still contained an appreciable quantity of penicillin. The excretion in this subject was slow and the total amount small. In the first 18 hours only 75 Florey units were excreted in the urine. This low figure, which is in distinct contrast to the excretion observed after intravenous injections of penicillin is partially explained by vomiting and renal suppression. The total amount found in the urine during the first 37 hours was about 10% of the administered dose.

When 5000 Florey units were injected into the lumbar area of another subject (No. 2), with rheumatoid arthritis, a concentration of 0.625 Florey unit per cc. of fluid was observed 26 hours after the injection. Excretion in the urine, although delayed, was in greater quantities than in Subject 1. The total excretion in the first 24 hours was 22% of the administered dose.

In Subject 3, with miliary tuberculosis and tuberculous meningitis, the intrathecal injection of 10,000 Florey units was followed by the appearance of appreciable amounts of penicillin in the blood stream for a period of 7 hours. The spinal fluid at 17 hours contained 0.078 Florey unit per cc. and the total excretion of penicillin amounted to 78% of the administered dose. In Subject 4 with pneumococcal meningitis, who received intravenous injections of penicillin in addition to 3000 Florey units intrathecally, the spinal fluid contained 0.625 Florey unit 24 hours later.

Subject 5, with brain abscess and meningitis secondary to chronic empyema, received 10,000 Florey units and subsequently showed penicillin in the blood serum during the 3 hours in which samples were taken. The spinal fluid contained significant amounts of penicillin for 27 hours. Excretion in the urine totaled 27% of the administered dose. Subject 6, with brain abscess, meningitis and chronic empyema, showed a significant concentration in the spinal fluid 24 hours after the injection of 10,000 Florey units.

The fact that penicillin appeared in the blood stream for several hours after the injection in patients with meningitis, together with the increased excretion observed, suggests that penicillin is absorbed more rapidly when the meninges are inflamed. The results obtained after the injection into closed cavities⁷ were similar to the observations made after intrathecal injections in normal subjects in that

absorption was slow and the total amount excreted in the urine was small. Further, significant amounts of penicillin remained in the spinal fluid for a period of 24 hours.

It has been demonstrated previously that the intravenous injection of penicillin is not accompanied by toxic reactions.⁷ If penicillin is to be injected locally in the treatment of infections of the brain and meninges, it is of great importance to know what toxic effects may be produced. The present study showed that an intrathecal injection of 10,000 Florey units in a normal subject was followed by nausea, vomiting and headache. At the same time there was an increased intrathecal pressure and a pleocytosis of 4170 per c.mm. of spinal fluid. When 5000 Florey units were injected into a normal subject, the only toxic symptom noted was a mild headache. There was a slight increase in the number of cells in the spinal fluid without an increase in the intrathecal pressure. In both subjects the leukocytes in the fluid were actively motile.

In the presence of meningitis or brain abscess the injection of 3000 to 10,000 Florey units was not attended by any toxic symptoms. One subject (No. 3) showed a slight increase in the spinal fluid pressure. All subjects showed a slight but definite increase in the number of cells in the fluid.

In general, then, the toxic reactions produced by intrathecal injections of 3000 to 10,000 Florey units are not severe, and this is especially true when 5000 Florey units or less are administered. The leukocyte response is similar to that observed after spinal anesthesia, lipiodol, serum or air injections.⁵

The observations made in 2 subjects (Nos. 4 and 5) showed that penicillin was present in significant concentrations in the cisterna magna and the third ventricle at the time of autopsy. This indicates that lumbar injections will result in a diffusion of the antibiotic agent throughout the ventriculo-subarachnoid space.

Penicillin has been shown to be extremely effective as an antibacterial agent against the streptococcus, pneumococcus and staphylococcus.^{1,3,4} Meningitis or brain abscess caused by the latter two organisms has been rather resistant to sulfonamide therapy.² It is suggested, therefore, that the intrathecal injection of penicillin may be effective in the treatment of these forms of meningitis, since an effective local concentration of the active substance can be maintained for a period of about 24 hours without undue toxic reactions. In general, the initial dose should not exceed 10,000 Florey units and subsequent doses of 5000 units each may be injected at intervals of 20 to 24 hours. If bacteremia is present, it is well to administer penicillin intravenously as well as intrathecally.

Summary. Data are presented concerning the blood and spinal fluid concentration and the urinary excretion of penicillin after the intrathecal injection of 3000 to 10,000 Florey units in normal subjects and patients with meningitis.

In normal subjects, penicillin was slowly absorbed and slowly excreted in the urine following the injection of 5000 or 10,000 Florey units. It was detected in the spinal fluid for 31.5 hours after the injection of 10,000 Florey units.

In subjects with meningitis, absorption of penicillin after intrathecal injection was more rapid than in normal individuals. Likewise, a greater amount of the administered dose was excreted in the urine. Penicillin was detected in the spinal fluid 24 hours after the injection of the antibiotic agent. In 2 subjects who died, penicillin was demonstrated in the cerebrospinal fluid removed from the third ventricle and from the cisterna magna.

In a normal subject the injection of 10,000 Florey units was followed by headache, vomiting, increased intrathecal pressure and phagocytosis in the spinal fluid. After the injection of 5000 Florey units no symptoms were noted other than a slight headache and a slight increase in the number of leukocytes in the spinal fluid. In subjects with meningitis no untoward symptoms were noted following the injection of 3000 to 10,000 Florey units.

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THE FIBRINOLYSIN TEST FOLLOWING HEMOLYTIC STREPTOCOCCAL INFECTIONS

By HERMAN YANNET, M.D.

MEDICAL DIRECTOR, SOUTHBURY TRAINING SCHOOL
AND

ALBERT LEIBOVITZ, M.S.

BACTERIOLOGIST, SOUTHBURY TRAINING SCHOOL,
SOUTHBURY, CONN.

TULLITT, Edwards and Garner¹ have demonstrated that the plasma clots of patients recovering from hemolytic streptococcal infections are resistant to the fibrinolytic activity of these organisms. Increasing utilization of the antistreptococcal fibrinolysin test has indicated its value in the diagnosis of probable cases of streptococcal fever, the tracing of streptococcal infections from the epidemiologic viewpoint, and in the investigation of sequelae of streptococcal diseases.

An outbreak of hemolytic streptococcal infections affecting 12

inmates of an institution for the mentally retarded, afforded an opportunity to study the effect of various factors on the incidence and persistence of plasma antistreptococcal fibrinolytic activity.

Procedure, Material and Methods. The inmates were housed in 15 cottages, each having a capacity from 25 to 60 beds. The patients contracting the infections lived in 10 of the cottages. At the onset of the disease, the patients were removed from their respective cottages, treated in the hospital until completely recovered, and then returned to their original cottages. Throat cultures were obtained routinely on all hospital admissions. Cultures from superficial skin lesions, nasal and vaginal discharges were obtained when these manifestations were noted. Only those individuals from whom the *beta* hemolytic streptococcus could be isolated, and who showed clinical evidence of streptococcal disease, were included in this study.

The first blood sample was obtained from 2 to 4 weeks following the onset of the acute infection. Subsequent samples were taken at approximately monthly intervals thereafter. At least 6 monthly examinations were carried out on all patients.

Rhinopharyngitis or tonsillitis was present in 25 patients; 3 had suppurative otitis media; 2 scarlet fever; 1 erysipelas; and 1 patient had streptococcal vaginitis with localized dermatitis. All patients recovered without any significant complications.

During the acute stage of the infection, the patients were treated symptomatically except for 9 cases, 5 of whom received sulfanilamide and 4 sulfathiazole. The dose of the sulfonamide drugs was calculated on the basis of approximately 1 gr. per pound, not exceeding 6 gm. per day.

The antistreptococcal fibrinolysin tests were performed according to the technique of Tillett and Garner⁸ as modified by Boisvert.¹ All tests were run in a 37° C. water bath and were arbitrarily terminated after 24 hours. The results were recorded as follows:

- 4+, no lysis in 24 hours.
- 3+, complete lysis in 8 to 24 hours.
- 2+, complete lysis in 3 to 8 hours.
- 1+, complete lysis in 1 to 3 hours.
- 0, complete lysis in less than 1 hour.

Three strains of *beta* hemolytic streptococci (Lancefield, Group A) were used. All were obtained from patients with acute pharyngitis and were capable of lysing normal human plasma clots in less than 15 minutes.

Results. The results have been summarized in the accompanying charts and tables. Chart 1 compares the age distribution of the patients with that of the inmate population of the institution. It will be noted that between the ages of 6 to 35 there is no special age group showing increased susceptibility to hemolytic streptococcal infections.

Chart 2 presents in graphic form the results of the antifibrinolysin tests. The results are shown as the percentage of the total number of patients who exhibited the different degrees of plasma clot resistance for each of the 6 months following the acute infection. Within 1 month after the onset of the infection, almost 80% of the patients had a plasma clot resistance of at least 24 hours duration. This value gradually decreased to about 5% by the 6th month. Tillett, Edwards, and Garner⁷ found that the plasma clots of "normal"

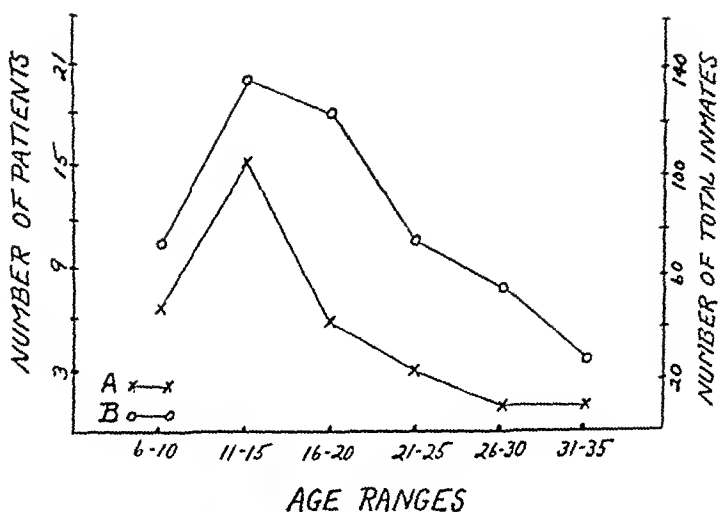
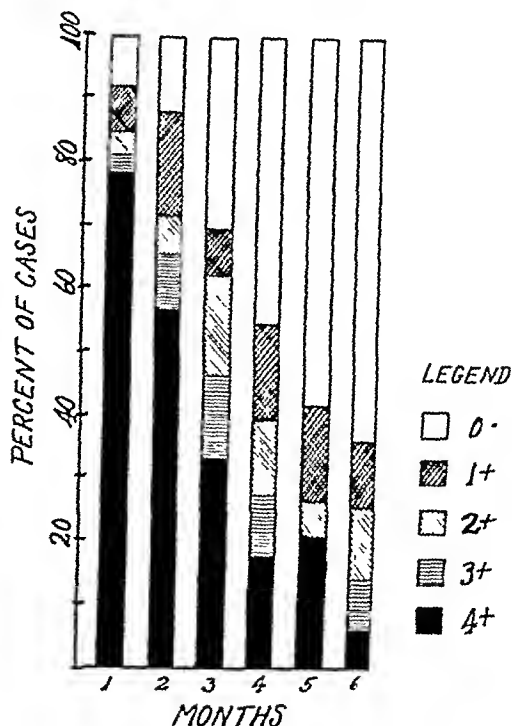


CHART 1 —Age distribution of patients as compared to that of total population.



0+, Complete lysis in less than 1 hour.

1+, Complete lysis in 1 to 3 hours.

2+, Complete lysis in 3 to 8 hours.

3+, Complete lysis in 8 to 24 hours.

4+, No lysis in 24 hours.

CHART 2.—Occurrence and persistence of anti-fibrinolytic resistance following acute hemolytic streptococcal infections.

persons, *i. e.*, those persons with no history of antecedent streptococcal infections, were completely lysed in 75% of the cases in less than 1 hour, and in every case in less than 4 hours. If we consider a clot resistance of 3 hours as the probable upper limit of "normal" resistance, it will be noted that as late as 4 months after the acute infection, 40% of our cases had maintained an increased clot resistance, and that 6 months after the infection about 25% of the patients continued to show an increased clot resistance. On the other hand, about 15% of the patients showed at no time during this study a significant increase in their clot resistance. The 5 patients in the latter group were diagnosed during their acute illness as follows: erysipelas, 1 case; streptococcal vaginitis and dermatitis, 1 case; acute otitis media, 1 case; and pharyngitis, 2 cases.

TABLE 1.—EFFECT OF AGE ON THE DEVELOPMENT OF ANTIFIBRINOLYTIC RESISTANCE

(Percentage of persons having plasma clots that resisted streptococcal fibrinolysis for more than 3 hours)

Age range	Months					
	1	2	3	4	5	6
6 to 13 yrs. ^{13*}	62	62	54	23	15	15
14 to 35 yrs. ¹⁹	90	75	65	50	33	35

* Number of cases.

Table 1 was prepared to show the effect of age on the development of plasma clot resistance. In this and subsequent tables, plasma clots that resisted fibrinolysis for at least 3 hours are considered positive. The values given are the percentage of patients in each group that exhibited positive tests during each of the 6 months covered by this study. Although the percentage of patients with positive tests was smaller in the younger group for each month, analysis of the results showed that the differences were not statistically significant (a difference between the two percentages of at least twice the standard deviation of the difference was considered significant).

Table 2 evaluates the effect of the duration of the acute infection on the development of plasma clot resistance. The patients were divided into 2 groups: those in which fever (100.6° F. or higher) was present for 3 days or less, and those in which the febrile period

TABLE 2.—RELATIONSHIP OF DAYS OF FEVER TO ANTIFIBRINOLYTIC RESISTANCE
(Percentage of persons having plasma clots that resisted streptococcal fibrinolysis for more than 3 hours)

Duration of fever*	Months					
	1	2	3	4	5	6
1 to 3 days ^{15†}	80	67	51	40	27	27
4 to 16 days ¹⁷	88	82	59	35	24	24

* 100.6° F. or higher.

† Number of cases.

persisted for more than 3 days. A comparison of the percentage of patients showing a positive test in each group for each of the 6 months yields no significant differences.

Discussion. Our observations on the incidence of the development of plasma clot resistance to the streptococcal fibrinolysin following proven cases of streptococcal disease is in agreement with the findings of others.^{1 6 7} From 15 to 25% of individuals recovering from streptococcal infections fail to develop plasma clot resistance. From the clinical aspect, there was nothing to distinguish these individuals from those in whom resistant clots were found. A special study was carried out to compare these individuals with the so-called "normals" who also exhibit rapidly lysing plasma clots. These studies will be reported in detail at a later date. However, it was not possible to demonstrate any significant differences in the sera or plasma clot between the individuals without a history of a recent streptococcal infection ("normals") and those individuals recovering from an acute streptococcal infection but not developing plasma clot resistance.

Except for isolated observations, there are no significant data available as to the effect of age on the ability of individuals to develop antifibrinolytic plasma clots. In order to obtain an adequate number of cases in each group for statistical analysis, the patients were divided into 2 groups with 14 years arbitrarily being chosen as the critical age. Under these conditions, no differences could be noted between the 2 groups as regards the incidence of positive antifibrinolysin tests. If we assume that the positive test represents an antibody response to a hemolytic streptococcal infection, the results obtained are in agreement with data previously published which also indicated that age (between 6 and approximately 10 years) had no significant effect on the development of the specific agglutinins following typhoid vaccinations; a similar finding was noted in the demonstration of the natural heterophile (sheep cell agglutinins).⁸

Perry⁹ found that of 15 individuals with a previous history of rheumatic fever who developed acute streptococcal throat infections, the administration of aspirin daily for 6 weeks was associated with the failure of 13 cases to develop plasma clot resistance. Similarly, of 6 cases with rheumatic heart disease who developed rheumatic relapses following streptococcal throat infections, the administration of aspirin was associated with the finding of negative antifibrinolysin tests in 4 patients. In our study, there were 13 patients that received aspirin during the acute stage of their infection. However, there was no evidence that this group in any way differed from those not receiving aspirin as to the incidence or persistence of a positive antifibrinolysin test. The explanation for this difference in results is not clear.

The administration of sulfonamide drugs during the acute phase

of the streptococcal infection apparently had no significant effect on the plasma antifibrinolytic activity. This is in agreement with the findings of Kirby and Rantz⁴ who carried out both *in vivo* and *in vitro* experiments to test this possibility.

No evidence was found that the duration of the acute phase of the original streptococcal infection, or its severity, was related to the subsequent development of antifibrinolytic activity. There are no similar data obtained from patients with streptococcal infections available in the literature for purposes of comparison. However, Perry⁶ and Boisvert² noted that individuals with acute rheumatic fever behaved similarly to patients recovering from streptococcal infections in that 75 to 85% of the cases in each group developed resistant plasma clots. These authors agree with Coburn and Pauli³ that rheumatic attacks may be initiated by a previous streptococcal infection. In those patients with acute rheumatic fever, Perry⁶ also found no correlation between the antifibrinolytic activity and the duration or the intensity of the infection. On the other hand, Boisvert² and Waaler⁹ concluded that this correlation did exist in their patients with rheumatic fever. It is apparent that further observations are needed before any definite conclusions can be drawn concerning this relationship.

Summary and Conclusions. A study of 32 individuals convalescing from acute hemolytic streptococcal infections was carried out. The observations may be summarized as follows:

1. Between the ages of 6 and approximately 35 years, there was no special age group showing an increased susceptibility to hemolytic streptococcal infections.

2. The antistreptococcal fibrinolysin test is positive (*i. e.*, the plasma clot resists lysis for more than 3 hours) in approximately 85% of the patients during the 1st month following the acute infection; in 65% during the 2d month; 60% the 3d month; 40% the 4th month; 25% during the 5th and 6th months.

3. The development of a positive antifibrinolysin test between the ages of 6 and approximately 35 years is not significantly influenced by age.

4. The duration and severity of the original infection is not significantly related to the subsequent development of increased clot resistance.

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THE SPECIFIC GRAVITY OF WHOLE BLOOD AND SERUM

BY P. A. GRAY, LIEUT.-COMM., M.C., U.S.N.R.

AND

A. H. ELLIOT, M.D.

SANTA BARBARA, CALIF.

(From the Research Department of The Santa Barbara Clinic)

THE following drop method for measuring the specific gravity of the blood, as described by Barbour and Hamilton,² affords a rapid and accurate estimate of the state of hydration as well as the serum protein content of the circulating blood. The technique is easily acquired and, as stated by the originators, the results are accurate to within $\pm .0001$, thus far exceeding the accuracy of other measurements, such as red cell and hemoglobin determinations, commonly used for this purpose. Some of the clinical applications of this procedure have been explored by Seudder;⁴ but as it has not come into the widespread use which it seems to deserve, an appraisal of our experiences of its application to the estimation of normal and pathologic states may be of interest.

Normal Values. The average serum specific gravity value of 194 specimens of blood obtained from 101 office patients with minor ailments, and individuals requesting premarital Wassermann tests, was $1.0266 \pm .0010$ (range 1.0242 to 1.0299). No differentiation as to sex was attempted. The distribution is plotted in Chart 1.

Variations of serum specific gravity from day to day in the same individual were extremely slight, as evidenced by an average of $1.0264 \pm .00036$ for 17 determinations in 1 young male (Table 1)

TABLE 1 —NORMAL SPECIFIC GRAVITY OF SERUM

No. of of cases	No. of determinations	Average	Range
101	194	$1.0266 \pm .0010$	1.0242-1.0299
N B	17	$1.0261 \pm .00036$	1.0260-1.0271
T G	16	$1.0264 \pm .00094$	1.0251-1.0281
E S (diabetic)	27	$1.0270 \pm .00095$	1.0252-1.0285

In a young female followed for 16 days, the average was $1.02636 \pm .00094$. The occurrence of menstruation during this period was without apparent effect. In a young, otherwise healthy, diabetic followed for a month, slightly greater variability was encountered which could not be correlated with the blood sugar level (Table 1)

These normal values, while based on a larger series than any previously reported, agree substantially with those of other observers and with the results obtained by other techniques (Table 2). The variation in values, although slight, encountered among normal individuals, far exceeds the error of the method. Theoretically, the serum specific gravity might vary with the water content of the

blood, the concentration of serum protein, or the concentration of lipids, catabolites and electrolytes. The influence of the first named is evident in pathologic states, to be discussed later. Moore and Van Slyke³ have shown that a straight line correlation exists between serum specific gravity and concentration of serum protein. It seems unlikely that the latter should change greatly from day to day. The effect of variation in electrolytes and other solutes is not known with certainty, but is probably not appreciable. We suspect, therefore, that the variations encountered represent primarily the effect of water shift between blood and tissues.

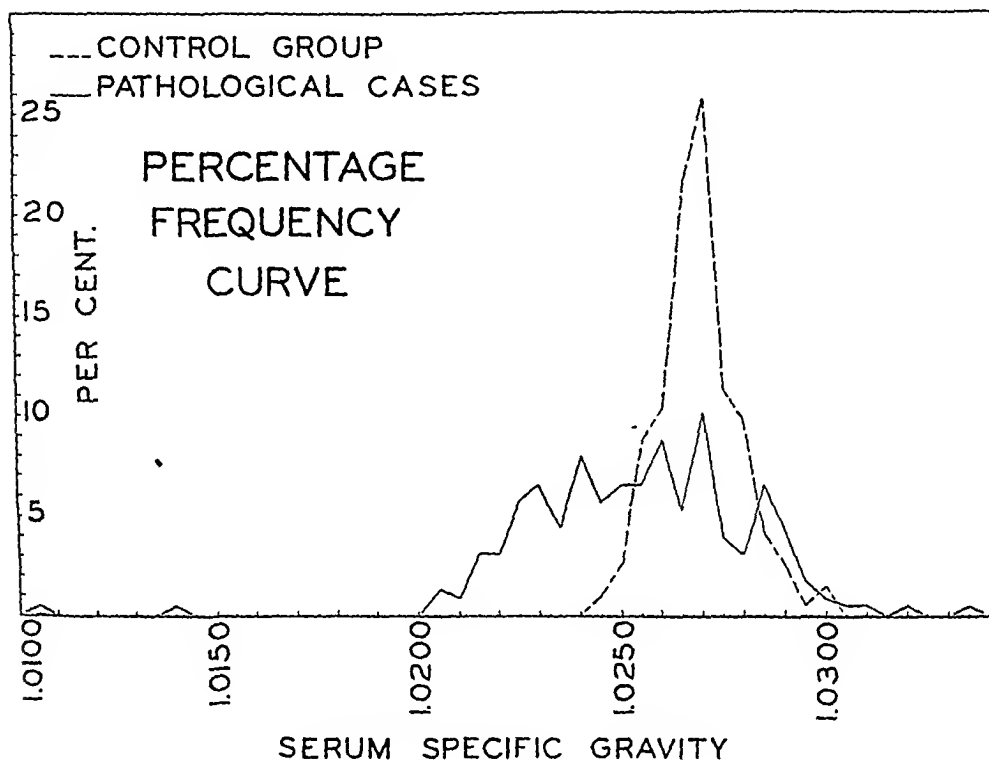


CHART 1

TABLE 2.—SERUM SPECIFIC GRAVITY

Author	Cases	Method	AV	SD	R
Moore-Van Slyke*	9	Gravimetric	1.0270	..	1.0253-1.0287
1930					
Ashworth-Adams†	20	Hematocrit	1.0261†	.00117	1.0240-1.0293
1941					
Gray-Elliot	101	Falling drop	1.0266	.0010	1.0242-1.0299
1941					

* Males only.

† Plasma.

‡ Recalculated.

AV = Mean value. SD = Standard deviation. R = Range of values.

The average whole blood specific gravity of 32 normal individuals averaged $1.0557 \pm .0020$. The range was 1.0501 to 1.0619 (Table 3). A close correlation between the number of red blood cells per c.mm.

and the whole blood specific gravity was apparent, as shown on the spot diagram (Chart 2).^{*} This obtained in both normal and pathologic states.

TABLE 3.—NORMAL SPECIFIC GRAVITY OF WHOLE BLOOD

No. of cases	No. of determinations	Average red cell count (millions)	Range (millions)	Average whole blood specific gravity	Range
32*	32	4.94 ± .51	3.92-6.15	1.0557 ± .002	1.0501-1.0619
20†	126	5.70 ± .64	4.05-7.00	1.0638 ± .0036	1.0577-1.0743

* Adults.

† Babies.

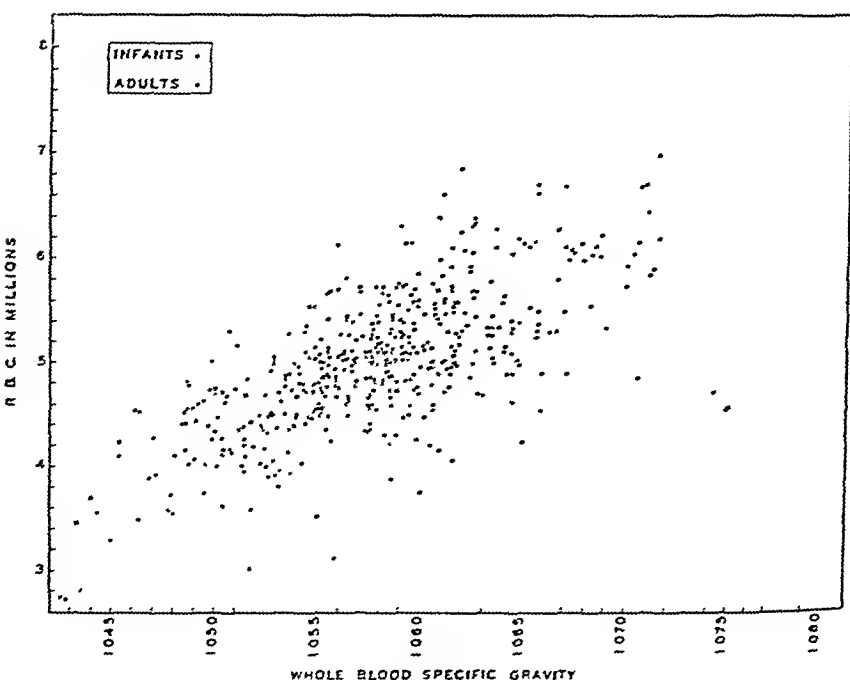


CHART 2

The Specific Gravity in States of Altered Physiology. Since the whole blood and serum specific gravity vary directly with the number of red cells and serum protein concentration respectively, any disease in which either constituent is altered will influence the corresponding specific gravity determination. It, therefore, follows

* Interpolation of our results in the Cartesian equation gave the following formulae:
Normal cases: Whole blood specific gravity = $1.044 \div 0.0023 \times \text{R.B.C. (in millions)}$.

Diabetics: Whole blood specific gravity = $1.0372 \div 0.0038 \times \text{R.B.C. (in millions)}$.

Newborns: Whole blood specific gravity = $1.0467 \div 0.0032 \times \text{R.B.C. (in millions)}$.

It will be seen that there is a slight but distinct difference in the slope of the linear correlation obtained from our data on normal adults, diabetics and newborns.

that the whole blood and serum specific gravity do not necessarily follow a reciprocal relationship. However, it is obvious that any change in the water concentration of the blood, since it affects the number of red cells as well as the serum protein, will be reflected by a proportionate rise or fall in both the whole blood and serum specific gravity.

Effect of Altered Red Cell Count. The average of 9 determinations of serum specific gravity on 3 patients with anemia was not significantly below the normal value ($1.0261 \pm .0006$), whereas the whole blood specific gravity values varied directly with the red cell count (Chart 2). In a case of polycythemia vera, having a hemoglobin of 19.2 gm. (115%) and a red cell count of 7.5 million, repeated observations of the serum specific gravity gave normal readings. Thus it appears that serum specific gravity and, hence by inference, the serum protein level are not influenced by the concentration of hemoglobin or cellular elements. The influence of physiologic polycythemia upon the whole blood specific gravity, however, is well exemplified by a study of the newborn, in whom definitely high values were encountered (Table 3).

Effect of Altered Serum Protein Concentration. It has not been possible to study instances in which serum protein values were increased, but it is of interest that in 5 patients with active allergic symptoms, slightly elevated serum specific gravity values were found (average $1.0283 \pm .0011$). Unfortunately, direct measurements of serum protein were not made, but as there was no reason to suspect dehydration in these individuals it seems safe to assume that slight hyperproteinemia was present. This merits further investigation. Low serum specific gravity values have been encountered in a number of patients having disorders commonly associated with hypoproteinemia. In 3 instances of portal cirrhosis, the values ranged from 1.0269 to 1.0226, averaging 1.0242 (= serum protein 5.88%). One patient with nephrosis had values from 1.0242 to 1.0201; in an eclamptic, a range from 1.0246 to 1.0206 was encountered. It is of interest that all but 2 of a group of 17 pregnant but healthy women showed slightly lowered serum specific gravity values irrespective of the duration of pregnancy (Table 4).

The effect of loss of serum protein by hemorrhage is illustrated by a serum specific gravity value of 1.0218 shortly after a sudden massive hemorrhage sufficient to reduce the number of red cells to 3.9 million and the hemoglobin to 11.3 gm. (67%). While some of this lowering was doubtless due to sudden dilution, regeneration of the serum protein was believed to be slow in comparison to cellular elements because the serum specific gravity reading had not changed after 14 days, although the red cell count had risen.

Conditions Influencing Water Content of Blood. States of chronic hydremia or anhydremia are probably uncommon due to the extraordinary efficiency of the mechanism for maintaining homeostasis.

We have observed an instance of diabetes insipidus, partially controlled with pituitary extract, in whom a state of anhydremia was apparently constant, the serum specific gravity on repeated determinations varying from 1.0267 to 1.0315. Depression of the re-sorptive capacity of the renal tubular cells with resultant blood concentration affords an adequate explanation, but it is surprising that this condition obtained in spite of an unlimited fluid intake. An alternative hypothesis, namely, that there was an actual increase in serum protein in this instance, unfortunately was not investigated.

TABLE 4.—SERUM SPECIFIC GRAVITY VALUES IN PREGNANCY

	Trimester	Specific gravity
E. C.	1	1 0236
J. C.	1	1 0260
D. A.	1	1 0253
A. B.	1	1 0253
P. F.	1	1 0236
C. H.	2	1 0227
D. T.	2	1 0289
C. C.	2	1 0240
G. H.	2	1 0237
L. J.	2	1 0256
H. O.	2	1 0255
G. S.	2	1 0242
J. M.	2	1 0254
C. Z.	2	1 0241
H. A.	3	1 0283
K. K.	3	1 0257
K. O.	3	1 0236

The diabetic state, particularly if uncontrolled, is known to disturb the water metabolism of the body, but a chronic state of hydremia or anhydremia, as measured by serum and whole blood specific gravity determinations on a large group of diabetic patients, has not been encountered (Table 5). The average values have been close to the normal, but the spread was greater as the group included some individuals in mild acidosis, in whom dehydration of some degree was probably present. The presence or absence of ketonuria and the level of the blood sugar did not consistently influence the specific gravity values.

TABLE 5.—SERUM AND WHOLE BLOOD SPECIFIC GRAVITY IN DIABETICS

	Serum	Whole blood
Number of cases	44	44
Number of determinations	99	212
Average red blood cells (millions)		4 97 \pm 68
Average serum specific gravity	1 0266 \pm 0019	
Range	1 0219-1 0333	
Average whole blood specific gravity		1 0560 \pm 0039
Range		1 0436-1 0667

Specific gravity determinations find their greatest clinical usefulness as an aid in the maintenance of proper body hydration in acute metabolic disturbances, as exemplified by the postoperative period. Seventy-two observations of serum specific gravity during the im-

mediate postoperative period of 14 subjects who had undergone major surgical procedures gave an average reading of $1.0239 \pm .0017$. We interpret this as indicative of a tendency toward hydremia, although the amount and type of fluid given in each instance was strictly in accord with usual clinical practice. While repeated determinations of the red cell count, hematocrit value, or serum protein concentration would have revealed this same tendency, these procedures are time-consuming, relatively inaccurate, and often too expensive to be repeated at short intervals. The practical application of specific gravity determinations to the care of the postoperative patient may be indicated by the following cases.

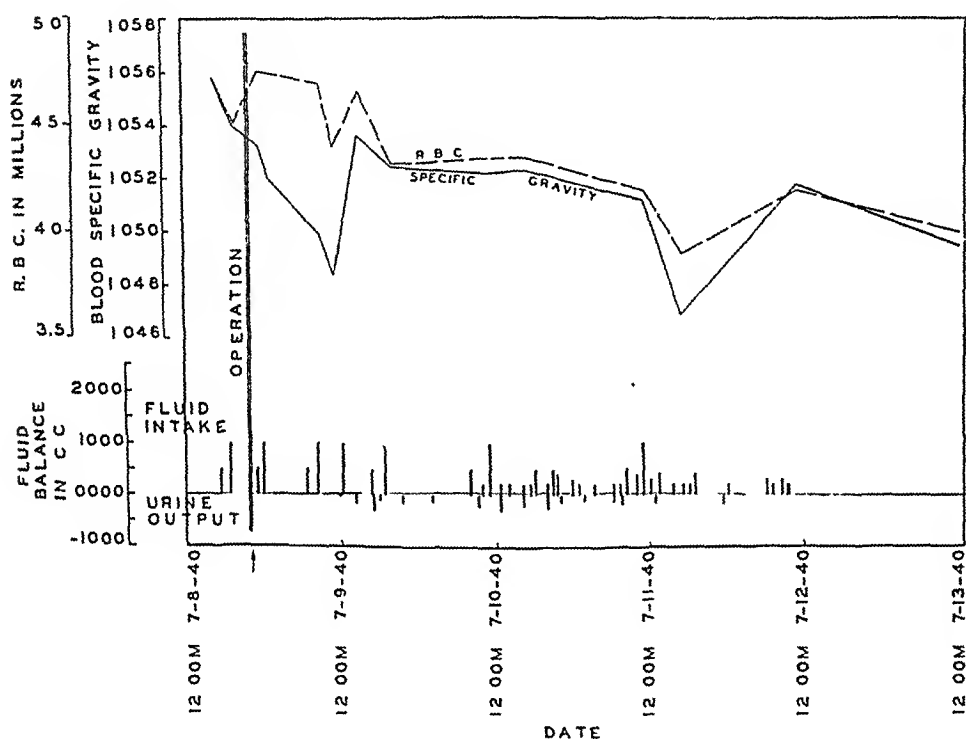


CHART 3

Case Abstracts. CASE 1. A white male, aged 59, a known mild diabetic, was admitted to the hospital July 8, 1940, with acute cholecystitis. The patient was in relatively good condition. As seen in Chart 3, his blood sugar measured 291 mg. per 100 cc., his carbon dioxide combining power was 69 vols. %. Ketonuria was absent. The whole blood specific gravity (1.0559), however, indicated slight dehydration. He was immediately given 500 cc. of Hartman's solution by venoclysis, and 1000 cc. normal saline by hypodermoclysis. During the operation that evening he received 500 cc. of 5% dextrose in normal saline. On the following morning a lower whole blood specific gravity indicated a satisfactory degree of hydration but the rising values later in the day and an extremely low urine output prompted the administration of more fluid. It will be noted that these changes were not accurately reflected by the red blood cell count which remained fairly constant. From the second day when fluids could be taken freely by mouth, the whole blood specific gravity and red blood cell values

remained fairly constant, as shown in the accompanying chart. Both the whole blood specific gravity and erythrocyte determinations were made at 2 hour intervals throughout the first day, at 4 hour intervals the second day, and twice daily thereafter.

CASE 2.—This case (Chart 4) is presented to show what degree and duration of change in the blood-water content may occur during the postoperative period when the usual routine administration of 3000 cc. of fluid during the first 24 hours is followed.

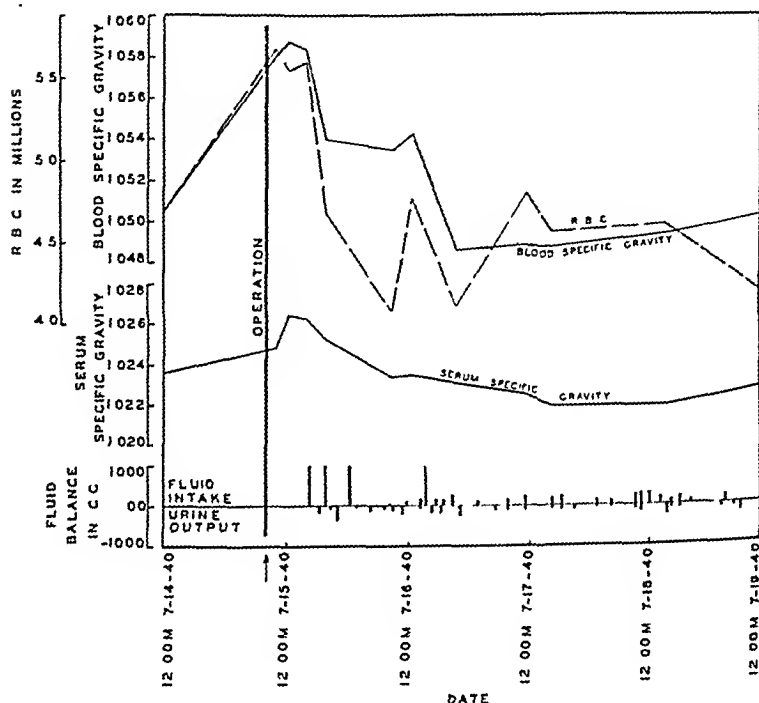


CHART 4

A white female, aged 70 years, was found by cholangiography performed 3 weeks after an uneventful cholecystectomy, to have a stone in the common bile duct. Choledocholithotomy was undertaken. Specific gravity studies were carried out as in the first instance but fluids were given irrespective of the specific gravity values obtained, and in accord with the usual practice of giving 3000 cc. in the first 24 hours. The chart shows that in comparison with the first case the magnitude and duration of change in the specific gravity values from the preoperative level was much greater. The curve may be interpreted as indicating that a state of relative anhydremia persisted over a period of 48 hours. This is in contrast to the first instance in which the water content of the blood was stabilized within 18 hours.

Since the prevention of postoperative complications may depend in some degree upon our skill in maintaining homeostasis, a rapid and reliable measurement, which helps to substitute rational adjustment of therapy for the rule of thumb procedure, is welcome.

Summary. 1. Normal values for serum and for whole blood specific gravity, obtained by the Barbour and Hamilton Falling Drop technique, were determined.

2. The influence of physiologic states, such as menstruation, pregnancy, age, daily individual variation, and so forth, was studied.

3. The influence of pathologic states in which variation from normal of certain blood constituents such as red blood cell, serum protein, and water content upon blood specific gravity determinations was observed.

4. The correlation between the red blood cell count and the whole blood specific gravity was determined.

5. The practical application of this technique to the estimation of fluid need in the postoperative state was illustrated and its value in treatment suggested.

We wish to thank Mr. Elihu Suits for technical assistance.

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CHEMICAL FRACTIONATION FROM EXUDATES OF A FACTOR PROMOTING LEUKOCYTOSIS

By VALY MENKIN, M.D.

ASSISTANT PROFESSOR OF PATHOLOGY, HARVARD UNIVERSITY MEDICAL SCHOOL
AND

M. A. KADISH, A.B.

with the assistance of A. A. WARREN, M.A.

BOSTON, MASS.

(From the Department of Pathology, Harvard University Medical School)*

EARLIER studies by one of us have demonstrated that inflammatory exudates contain a leukocytosis-promoting factor capable of eliciting a discharge into the circulation of immature polymorphonuclear leukocytes from the bone marrow.¹ The resulting leukocytosis appears relatively early and remains sustained for at least several hours. The leukocytosis-promoting factor (denoted LPF) was subsequently found to be apparently a pseudoglobulin.² The factor was recovered from exudative material derived from dogs, rabbits and man.^{1,2,3,4} The inflammatory reaction from which the exudates were derived was induced by a variety of unrelated

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irritants. These studies on the presence of a leukocytosis-promoting factor in exudates of rabbits have received confirmation in the hands of Reifstein and his collaborators.⁸ Further studies have indicated that the active globulin can be demonstrated to be present only in the blood serum of animals having a concomitant inflammatory reaction.⁵ This supports the view that the factor is liberated at the site of inflammation and evidently reaches the bone marrow *via* the circulating blood.

These various studies have offered a reasonable explanation for the mechanism of leukocytosis associated with various inflammatory processes. Inasmuch as the prognosis of numerous infectious conditions is referable to the number of circulating leukocytes,⁹ it is conceivable that the LPF may yet prove to be of clinical significance. For this reason an attempt has been made to obtain the active fraction in a desiccated form which could be conveniently handled, and yet which could maintain its potency as well as its stability. In a preliminary earlier report, one of us has reported on the feasibility of such a preparation.⁶ The present brief communication represents additional data to substantiate this preliminary finding.

Method. Exudates were generally obtained, as described in previous reports,^{1,2} by inducing an acute pleural inflammation in dogs with the injection of about 1.5 cc. of turpentine. In several instances exudative material was also obtained from either the pleural or the peritoneal cavity of human patients.

The method of preparing the LPF in desiccated form has been briefly described by one of us in a preliminary note⁶ and is briefly restated here: The exudate is treated with saturated ammonium sulphate so as to induce precipitation at half saturation. The precipitate is not readily separated from the supernatant phase by ordinary centrifugalization. For this reason the whole mixture is dialyzed for about 24 hours against running tap water.* On the following day the indiffusible material is reprecipitated with ammonium sulphate at half saturation. Prolonged centrifugalization now yields moderately good separation. The precipitate is taken up in distilled water and dialyzed against tap water until it is free of SO_4 . The indiffusible material is then dried at about 35° C. in a vacuum oven to a brittle crystalline-like faintly brownish powder. The process of desiccation does not seem to impair the potency of the material, for biologic activity was found apparently unaltered in such fractions several months following their preparation.

Approximately 100 mg. of the fraction containing the LPF was taken up either in saline or in a phosphate buffer at pH of about 7.4 and injected into the circulating blood by cardiac puncture.[†] Several dogs were also

* This amount of the fraction was roughly estimated to be the equivalent of about 20 to 25 cc. of the original exudate. In some experiments considerably larger amounts of the fraction were injected but the effect on the leukocyte level was not correspondingly enhanced. In further purified fractions (unpublished studies), 13 to 15 milligrams were found sufficient to induce a marked leukocytosis.

† In an earlier preliminary note another step was introduced here, namely, treatment with ether presumably to remove the lipoprotein fraction.⁶ Subsequently it was found that omission of this step does not impair the potency or stability of the material. Furthermore, as pointed out below, elimination of the euglobulin fraction favors the production of a more active fraction (unpublished studies).

injected subcutaneously with the material. Leukocyte counts were made at approximately every hour for periods ranging from 6 to 13 hours. On the subsequent days several counts were made, and such measurements were usually continued until the original basal leukocytic level was attained. Blood samples for the counts were obtained by nicking with a razor the small vessels of the ear.

Results. In earlier studies repeated counts were performed in order to ascertain the range of normal variation in the absolute number of circulating leukocytes for a period that approximated the usual duration of an experiment.^{1,2} In one such series the maximum fluctuation in the leukocyte counts was found to average 23.8%.¹ In a subsequent series the increase was found to average 26.2%.² Such a test was likewise made in the present studies. The data appear in Table 1. It is clear that the degree of variation is of about the same magnitude as in earlier studies. The maximum increase in the number of circulating leukocytes of untreated dogs over a period ranging from 5 to 13 hours averages 29.2%.

TABLE 1.—VARIATION IN WHITE CELL COUNTS ON BLOOD OF NORMAL DOGS

Dog No.	Lowest number of leukocytes within a period ranging from about 5 to 13 hours (per c.mm.)	Highest number of leukocytes within a period ranging from about 5 to 13 hours (per c.mm.)	Increase in leukocytes (%)
7-19	6,500	11,600	78 5
7-31	13,000	17,850	37 3
4-73	11,050	13,750	24 4
7-33	15,750	18,600	18 1
7-18	13,250	15,600	17 7
7-19	9,900	11,500	16 1
7-31	18,400	20,600	12 0
Average	12,550	15,643	29 2

TABLE 2.—EFFECT OF THE LEUKOCYTOSIS-PROMOTING FACTOR (DESICCATED FORM) ON LEUKOCYTE COUNTS

Dog No.	Absolute number of leukocytes prior to injection of material (per c.mm.)	Highest level of leukocytes within about 4 to 10 hours after injection of material (per c.mm.)	Increase in leukocyte count (%)
7-19	12,150	31,750	161 3
7-19	8,550	21,950	156 7
7-31*	9,900	22,400	126 3
7-18	8,150	16,900	107 4
7-31*	11,650	22,600	94 0
4-73	12,650	20,950	65 6
7-31*	18,450	30,500	65 3
7-31	13,150	21,400	62 7
4-73	15,150	24,300	60 4
7-19	15,000	23,750	58 3
4-73	12,750	20,150	58 0
7-18	15,150	23,150	52 8
4-73	15,950	23,950	50 2
Average	12,973	23,365	86 1

* LPF extracted from human exudates; all others obtained from pleural exudates of dogs.

The effect on the leukocyte level induced by the LPF in desiccated form is of the same order as in earlier observations.^{1,2} The results of all experiments appear in Table 2. There is a significant increase of 86.1% in the number of circulating leukocytes. This represents a conspicuous rise above the effect of normal variation (Tables 1 and 2). The fractions obtained from human exudate proved to be as effective as those derived from dogs. A comparison of the effect of 50 cc. of whole exudate obtained from a patient with that of the desiccated fraction extracted from the same exudative material is

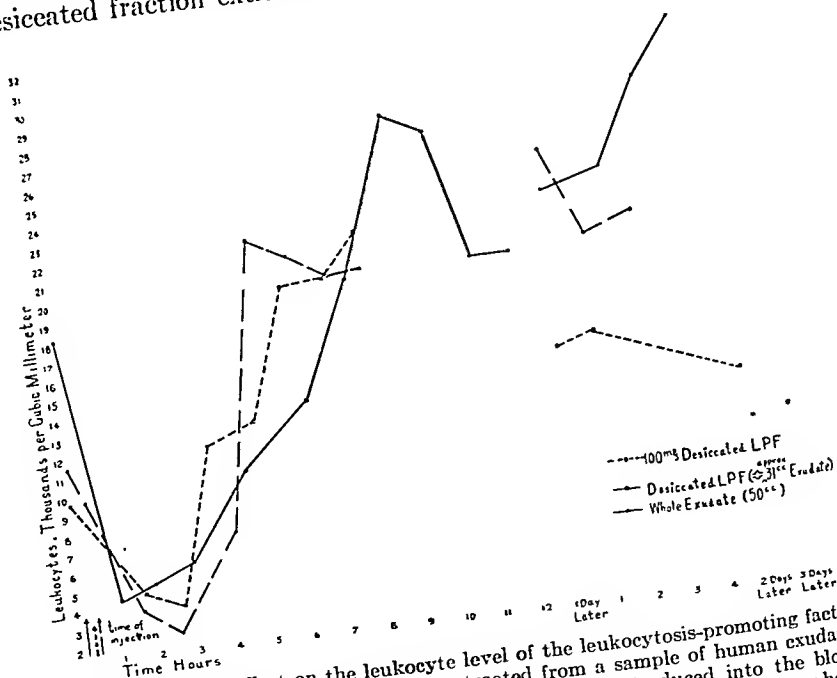


CHART 1.—The effect on the leukocyte level of the leukocytosis-promoting factor in desiccated form. The material was extracted from a sample of human exudate. —o—o About 100 mg. of the desiccated material was introduced into the blood stream of Dog 7-31. —o—o—o The desiccated material equivalent to about 31 cc. of exudate was injected into the same dog on a different day. —●—●—● Fifty cubic centimeters of whole exudate injected likewise into Dog 7-31 on a subsequent day. Note that the effect on the leukocyte level of these 3 fractions is in general of the same order of magnitude.

shown graphically in Chart 1. It is clear that the rise in circulating leukocytes is in both cases of about the same magnitude. It is to be noted that there may be an initial transient leukopenia immediately following the introduction of the active material. This temporary drop has been encountered previously.¹ The reason for the initial leukopenic manifestation is not clear. It is conceivable that it may be referable to some toxic impurities. The induced leukocytosis by the LPF may be sustained for as long as 24 hours (Chart 1).

In several experiments, the LPF in desiccated form was injected subcutaneously in the thigh of dogs. In general, introduction of about 100 mg. of the material by the subcutaneous route induced

TABLE 3.—EFFECT OF LPF (DESICCATED FORM), INJECTED SUBCUTANEOUSLY, ON LEUKOCYTE COUNTS

Dog No.	Absolute number of leukocytes prior to injection of material (per c.mm.)	Highest level of leukocytes within about 6 to 24 hours after injection of material (per c.mm.)	Increase in leukocyte count (%)
7-33 . . .	7,200	17,750	146 5
7-31 . . .	10,500	20,700	97 1
7-33 . . .	15,900	30,800	93 7
7-34 . . .	7,650	12,750	66 7
7-34 . . .	8,750	13,550	54 9
7-31* . . .	21,150	32,000	51 3
7-31† . . .	11,750	11,850	1 0
Average . . .	11,843	19,914	73 0

* LPF derived from canine exudate; all others were of human origin.

† Considerable local inflammation developed at site of injection of LPF.

somewhat similar results as described above (Table 2). The maximum effect, however, was sometimes found to appear somewhat later than when the material was introduced directly into the cir-

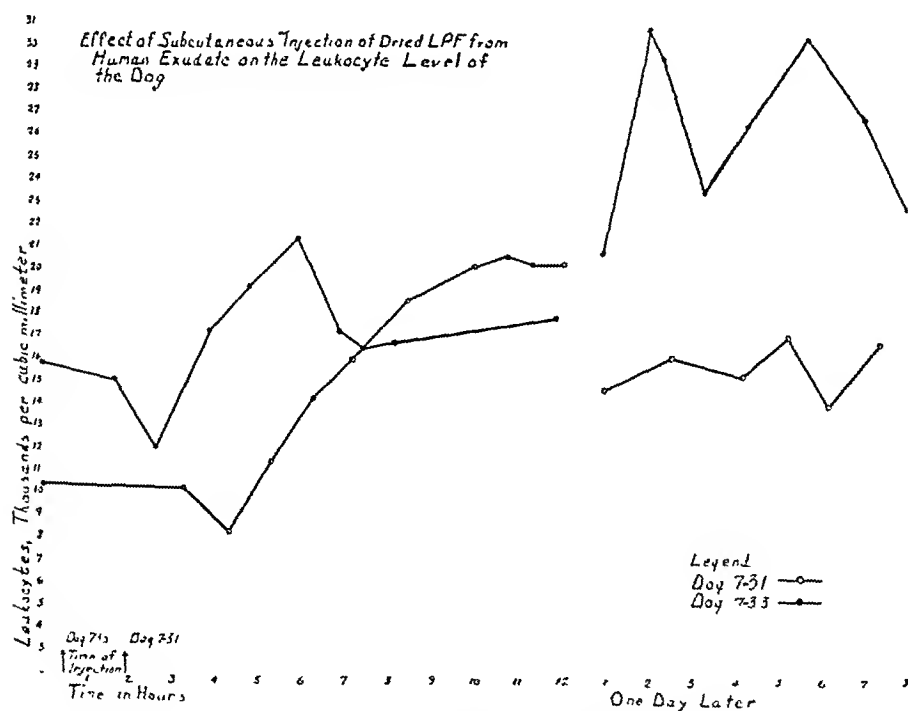


CHART 2.—The effect of subcutaneous injection of the dried LPF obtained from human exudate on the leukocyte level of dogs.

culating blood. This is quite likely referable to differential rate of absorption from the site of injection. The effect of such experiments (Table 3) is shown graphically in Chart 2. Furthermore, it is to be

noted that Dog 7-31 at one time failed to yield a rise in the number of circulating leukocytes following subcutaneous injection of the LPF (Table 3). Concomitantly with this lack of response there was found a pronounced inflammatory reaction at the site of injection. Inflammation is characterized by marked proteolysis.⁷ It is conceivable, therefore, that the LPF might have been hydrolyzed by proteolytic activity at the site of the developing inflammation in the subcutaneous tissue. It is also possible that the material was fixed *in situ* by the acute inflammatory reaction and thus failed to penetrate readily into the blood stream.⁴ These two explanations would perhaps adequately account for the failure of response in this particular experiment. Studies are in progress in an endeavor to purify further the LPF from the possible presence of impurities which may account in part for the occasionally marked local inflammatory reaction when the material is injected subcutaneously and perhaps also for the transient initial leukopenia when it is introduced directly into the circulation.*

Conclusions. Earlier observations have demonstrated the presence of a leukocytosis-promoting factor (LPF) in inflammatory exudates of various experimental animals and man.^{1,2,3} Subsequent chemical studies have shown this factor to be associated with the pseudoglobulin fraction of exudates.² The active globulin penetrates into the circulation from the site of inflammation and eventually induces a discharge of immature leukocytes from the bone marrow.⁵ This active factor can be readily desiccated. In the dried form it maintains both its potency and its stability for many months. The effect on the number of circulating leukocytes can be readily elicited by intravascular and to some extent by subcutaneous administration.

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ERYTHROBLASTOSIS FETALIS AND THE BLOOD FACTOR RH

By DONALD H. KARRHER, M.D.

INSTRUCTOR IN OBSTETRICS AND GYNECOLOGY AND ASSISTANT OBSTETRICIAN AND
GYNECOLOGIST, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE
AND DENTISTRY AND STRONG MEMORIAL HOSPITAL

AND

HOWARD A. SPINDLER, M.D.

RESIDENT OBSTETRICIAN AND GYNECOLOGIST, STRONG MEMORIAL HOSPITAL
ROCHESTER, N. Y.(From the Department of Obstetrics and Gynecology, University of Rochester School
of Medicine and Dentistry)

THE presence in the blood of the agglutinin Rh was first described in 1940 by Landsteiner and Wiener.¹ The close relationship of this agglutinin to the development of erythroblastosis fetalis was pointed out by Levine, Katzen and Burnham.⁴ Since then other articles have appeared which have corroborated this finding. The purpose of this paper is to report 6 cases of erythroblastosis fetalis which lend support to the thesis of isoimmunization of the mother by the Rh agglutinin from the fetus as being responsible for erythroblastosis fetalis of the latter.

Methods. Testing for the Rh factor is a delicate procedure, and has been fully described several times.^{1,2,4,5,6} The method of testing for the presence of anti-Rh substance when Rh- bloods are found is also described in the above articles.

Cases and Discussion. CASE 1. Mrs. S.* is a 31 year old para i, gravida iv, Wassermann negative. Her obstetric history is of interest. The first pregnancy ended with the full-term spontaneous delivery of a normal female infant 10 years ago. The second pregnancy, 3 years ago, terminated in a full-term male infant, following a very short precipitate labor. The infant died 3 days after birth. The patient was told by her physician that the cause of death was "jaundice." The 3d pregnancy, one year ago, resulted in a full-term stillborn female infant, labor again precipitate. The patient felt life until onset of labor. The 4th pregnancy was complicated by a moderately severe toxemia. The patient felt life again until the onset of labor, which was at term, and on October 20, 1941 she delivered a stillborn female infant. Unfortunately an autopsy on the infant was not obtained, nor was the placenta examined microscopically. No blood was obtained from the infant. However, the description of the baby was the classical one of congenital hydrops of the newborn. The baby was described as being extremely edematous, the edema of the face being so extreme that the optic apertures could not be found except after considerable search.

We obtained a sample of blood from Mrs. S. 24 hours after delivery and found her blood to be Group O Rh-. The serum was tested for anti-Rh and we found a titer of 1:64. (We sent some of this blood to Dr. Alexander Wiener who confirmed our findings.) The husband's blood was found to be Group A Rh+. Blood drawn from Mrs. S. on January 10, 1942, 10 weeks after delivery, contained no anti-Rh substance.

* We are indebted to Dr. S. B. Peters of Silver Creek, N. Y., for the history and blood samples on this patient.

We can conclude then from this case, even though we have no concrete evidence from the infant in the way of blood Rh determinations, blood smears, autopsy, or placental sections, that the infant probably suffered from the congenital hydrops type of erythroblastosis fetalis, and it is probable that the p resulted in infants which had one of the types of conclusions are based on the fact that the father's blood was Rh+, the mother's Rh- with a very high titer of anti-Rh substance in her blood 24 hours postpartum, which was entirely gone 2½ months postpartum. The most likely explanation of these findings is that the infant immunized the mother against the Rh factor by the transmission of the Rh agglutininogen found in the fetal red blood cells, across a faulty functioning placenta. Once the agglutininogen gained entrance into the maternal circulation reaction was begun, and the mother formed an anti-Rh isoantibody then passed through the placenta to the fetus and hemolyzed the fetal red blood cells, resulting in the development of erythroblastosis. The reason, of course, that no anti-Rh agglutinin was found in the mother's serum 10 weeks postpartum is that the immunologic stimulus had been removed with the termination of the pregnancy, and the isoantibody thereafter gradually disappeared from the maternal organism.

This case also serves to suggest the operation of the anamnestic reaction, *i. e.*, the exaggerated response to repeated antigenic stimuli. We see in reviewing the history that this patient had first a normal infant, then an infant who lived 3 days, next a stillbirth and finally a stillborn infant with congenital hydrops.

CASE 2. Mrs. I. M., a 19 year old para i, gravida ii, Wassermanu negative. In November 1940 this patient delivered spontaneously in this hospital a full-term normal female infant. On November 27, 1941 she was admitted to the Gynecological Service with a diagnosis of pregnancy and acute gonorrheal cervicitis. The expected date of confinement for the pregnancy was December 1, 1941. On routine blood examination she was found to have a Group A Rh- blood, with serum containing anti-Rh substance. The titer of this was 1:16. From this it was suspected that she would deliver an erythroblastotic infant. That our surmise was correct is of importance, because we were able before delivery to have a list of Rh-donors available, so that transfusion could be started as soon as it seemed necessary.

The patient was cured of her gonorrheal infection with sulfathiazole therapy and discharged from the hospital. She was readmitted December 22, 1941, and following a 22 hour labor was delivered by breech extraction of a living 3260-gm. female infant. The baby cried after a little resuscitation and appeared to be normal save for the very yellow color of the vernix caseosa. The icterus index on the cord blood was 44. Grouping on the cord blood showed the baby's blood to be Group A, Rh+, and there was no anti-Rh agglutinin demonstrable. The day after the birth a smear of capillary blood obtained by heel puncture showed 94 nucleated R.B.C./100 W.B.C. and many basophilic R.B.C. R.B.C. count 1.91 million, hemoglobin 8.8 gm., W.B.C. count 103,800. Subsequent developments proved conclusively that the infant was suffering from erythroblastosis. Table 1 shows the clinical course and laboratory data on the infant until its discharge from the hospital. Unfortunately blood from the father of this baby is not available for testing but it is safe to assume that it would be Rh+.

Here again then, is another case in which we have an erythroblastotic baby which is Rh+, with an Rh- mother in whose serum the anti-Rh agglutinin was demonstrable.

TABLE 1.—SHOWING CLINICAL COURSE OF ERYTHROBLASTOTIC INFANT TREATED WITH RH BLOOD TRANSFUSIONS (SEE CASE 2)

Date	Type	Rh	Cc. given	Reaction	RBC count	Hb., gm.	WBC count	Smear	Icterus index	Remarks
12/23/41	.				1 7	7 0			44	Day of birth
12/24/41	O	—	60	None	1 91	8 8	103,800	94 nucleated rbc per 100 wbc; many basophilic rbc	.	Marked icterus; edema of hands and feet; spleen 2 cm. below c.m.; liver border just below c.m.
12/24/41	O	—	50	None	2 63	10 5				
12/25/41	O	—	50	None	3 51	13 0	34,000	90 nucleated rbc per 100 wbc		
12/26/41					5 00	17 0		116 nucleated rbc per O.I.F.		
12/27/41	O	—	50	None	3 17	13 4	10,600	1 nucleated rbc. per 15/20 O.I.-F.		
12/28/41	.				3 8	15 0		No nucleated rbc		
12/30/41	O	—	75	None	3 05	9 7	10,800	..	32	Icterus clearing
12/31/41					3 7	10 8	10,400			
1/ 1/42	O	—	45	None	3 9	11 6				Icterus entirely gone
1/ 2/42	.					12 0				Liver and spleen just palpable
1/ 5/42					3 7	11 2	10,200	No nucleated rbc		Spleen not felt
1/20/42					3 7	11 1	11 000	No nucleated rbc		
1/22/42										Discharged; weight, 3400 gm.

Probably the most important point to be learned from this case is that neither the mother's nor the father's blood should be used to transfuse the infant. That this idea is not new with us, we subsequently learned. Levine and his co-workers³ first suggested this form of treatment. The mother's blood, if given to the infant would be merely prolonging the detrimental effects of the infant's intra-uterine life because, although the infant would be receiving red blood cells, it would also be receiving more anti-Rh substance which would certainly bring about the further destruction of the infant's own Rh+ cells.

As for transfusion with the father's blood, it is safe to assume that in many cases after birth the infant must still carry over some of the anti-Rh substance which it derived from the mother while *in utero*. It may be in the plasma, in concentrations too low to be detected by our present-day methods, or it may be primarily lodged in the spleen and in the reticulo-endothelial system in particular, so that it would escape detection by blood test. At any rate it probably continues to exert its damaging effect on the infant's Rh+ cells for a considerable time after birth, as evidenced by the development of icterus and a declining red blood cell count and hemoglobin value. Transfusing the infant with the father's blood would of course supply much needed red blood cells, but since

these cells are Rh+, some, if not all, would eventually be destroyed by the anti-Rh substance which the infant still had in its body.

Hence the value of using Rh- blood in transfusing these infants is obvious. It must be remembered, however, that the blood must be from an individual who has previously been tested for anti-Rh substance and found not to carry any of this agglutinin in the circulating blood. This precaution, however, is not necessary for male donors who have never themselves received a blood transfusion. The advisability of maintaining a list of Rh- donors need not be stressed.

CASE 3. Mrs. M. M.,* a 39 year old para i, gravida viii, Wassermann negative. The obstetric history is summarized in Table 2. This patient presents a fairly typical history of repeatedly giving birth to erythroblastic infants. Out of 8 pregnancies, she has only 1 living child—her first. We obtained blood from the patient and her husband during the 4th month of the last pregnancy. At this time the patient was found to be Group A, Rh- with anti-Rh substance present in her serum. The husband was Group O, Rh+. About 1 month after this examination the patient aborted an icteric 5 months fetus. Six weeks later, her serum was found to no longer contain any anti-Rh substance.

TABLE 2.—OBSTETRICAL HISTORY OF CASE 3

Pregnancy		Duration	Infant	Jaundice	Placental weight
No.	Yr.				
1	1926	Term	Alive	Several days	22 oz.
2	1927	Twins at 8½ months	Alive—died on 4th and 5th days	At birth	
3	1928	Term	Macerated		2 lb. 3 oz
4	1929	8½ months	Stillborn		3 lb. 3½ oz
5	1932	7½ months	Alive—died on 4th day; autopsy—icterus gravis	At birth	634 gm.
6	1935	3½ months	Spontaneous abortion		
7	1937	6 months	Alive—died on 3d day	At birth	
8	1941	5 months	Stillborn	At birth	

Unfortunately we were unable to test the blood of the fetus, but the presence of anti-Rh substance in the mother's blood during the pregnancy, and its absence 6 weeks following the termination of the pregnancy, would seem to point to the pregnancy as the etiology of the anti-Rh substance in the maternal circulation.

CASE 4. Mrs. R. H., a 31 year old para 0, gravida ix, Wassermann negative with an obstetric history as summarized in Table 3. Our blood studies on this patient, her husband, and the fetus are shown in Table 4.

This patient was catalogued in our case histories as a habitual aborter. However, it is unlikely that this diagnosis is correct, if we consider a habitual aborter as one in whom there is an insufficiency of progesterone. Perhaps a survey of our cases of habitual abortion would be in order. It is just possible that some of them would turn out to be just such a case as this one.

It is of interest that as early as 2 months prior to the termination of the pregnancy, we obtained a definite reaction for anti-Rh substance in the mother's serum. Three weeks later we were unable

* We are indebted to Dr. J. K. Quigley for the opportunity of studying this patient.

to detect the presence of this agglutinin, nor did we find it present in any of the subsequent tests up to the time of delivery. To our minds this does not definitely exclude the presence of the agglutinin in the serum at the time of the negative tests. Levine *et al.*³ have pointed out that the course of antibody production in general is a period of gradual increase, followed by a period of maximal activity, then gradual decline, and that probably in some cases anti-Rh agglutinins, after exerting their lytic effect on the fetus, rapidly disappear from the blood so that none can be demonstrated at the time of delivery. This type of mechanism may have been in play in our case. However, we think it more likely that the agglutinin is present in the serum, but we are unable to detect it by our present technique.

TABLE 3.—OBSTETRICAL HISTORY OF CASE 4 (NOTE TRANSFUSION REACTIONS WITH 8TH PREGNANCY)

Pregnancy		Duration	Infant
No.	Year		
1	1928	5 months	Stillborn
2	1931	Term	Lived 1½ days
3	1932	Term	Stillborn
4	1935	Term	Macerated
5	1936	Term	Stillborn
6	1938	5 months	Stillborn
7	1939	2 months	Stillborn
8	1941	8 months	Macerated
Trans- fusion No. 1	Donor (Husband)	Cc. 100	Reaction
	Group A Rh+		Precordial oppression; hot;
	Group O Rh+	450	flushed; chills; Temp. 39.6°C.
No. 2	Group O Rh+		Headache; dizziness; heaviness
No. 3	Group A Rh-	650	in chest; chills; dyspnea
			No reaction
9	1941	6 months	Stillborn—fetal heart not heard after 12 hours of labor; pale —waxlike skin; protuberant abdomen; placenta — large, pale; autopsy—erythroblas- tosis; placenta—erythroblas- tosis

TABLE 4.—BLOOD STUDIES ON CASE 4

Date	Group		Rh	Anti Rh
10/ 9/41	Patient	A	0	0
10/15/41	"		..	=
10/28/41	"		..	+
11/17/41	"		..	0
12/ 9/41	"		..	0
12/25/41	Delivered 6 month stillborn fetus			
12/25/41	Fetus ?	A	?	?
12/27/41	Patient		..	0
12/27/41	Husband	A	+	
1/ 3/42	Patient		..	0

Unfortunately we were unable to test for the Rh factor in the infant's serum. A postmortem cardiac puncture was attempted and a large amount of pink watery serum was withdrawn by syringe. Testing this for the Rh factor resulted in a negative test. However an autopsy subsequently showed that we had not entered the heart at all, but had merely tapped a pericardial effusion. By the time we learned of this no blood was available from the infant, so the test could not be repeated. The autopsy findings confirmed our diagnosis of erythroblastosis fetalis as did the gross and microscopic appearance of the placenta.

Another interesting bit of evidence is brought out in this patient's 8th pregnancy (Table 3). She was moderately anemic on admission to the hospital and in addition had a rather brisk postpartum hemorrhage, so that transfusion was definitely indicated. On the day of delivery the patient was transfused with the husband's blood (Group A, Rh+), but the transfusion had to be stopped after 100 cc. had been given because the patient complained of a sense of precordial oppression. Within a few minutes the patient became hot and flushed and had a severe chill, with the temperature reaching 39.6° C. Later on the same day a second transfusion was given from an apparently compatible Group O, Rh+ donor. This transfusion likewise had to be stopped after 450 cc. of blood had been given because of the development again of heaviness in the chest, headache, dizziness, dyspnea and chills. Two days later a third transfusion was given from a Group A, Rh- donor. This transfusion of 650 cc. was without harm, demonstrating that this donor was truly compatible.

The logical conclusion drawn from this chain of events is that the patient had an anti-Rh agglutinin in her serum, which reacted with the Rh+ cells in the first 2 transfusions resulting in transfusion reactions, but did not react with the Rh- cells in the third transfusion.

CASE 5. Mrs. M. S., a 27 year old para ii, gravida ii, Wassermann negative, delivered in this hospital in 1939 a full-term male infant which was perfectly normal. In 1939 she delivered at home a full-term infant which on the 2d day of life developed severe jaundice. The 3d day of life the infant suffered from convulsions and was brought into the hospital. Examination at the time showed intense icterus, liver and spleen enlarged. Blood count: R.B.C. 1,500,000; W.B.C. 14,000; Hb. 10 gm. Smear showed many nucleated red blood cells. The infant was transfused with 50 cc. of the father's blood. Death occurred about 3 hours later. Autopsy diagnosis was icterus gravis.

This patient again became pregnant in June 1941. We first examined her blood in October 1941 and found her to be Group O, Rh- with no anti-Rh substance in her serum. Six examinations of her serum between October 1941 and the time of delivery, March 22, 1942, failed to show any anti-Rh substance. On the latter date a normal 2790 gm. female was delivered spontaneously. Study of the cord blood showed the infant to be Group O, Rh+. The husband is also Group O, Rh+. Blood count on the infant showed R.B.C. 4,250,000; Hb. 16 gm., with a normal smear. Within the first 24 hours of birth the infant developed a severe icterus

(icterus index 192 units) and the hemoglobin fell to 11.6 gm. on the 5th day of life. The infant was given 3 transfusions of Group O, Rh- blood, the total amount transfused being 120 cc. From the first transfusion until the time of discharge on the 12th day of life the R.B.C. count and the hemoglobin gradually rose until at the time of discharge from the hospital the red blood cells were 4,100,000 and the hemoglobin 13.6 gm. Sinear normal. Diagnosis was hemolytic anemia of the newborn.

To return now to our study of the mother's serum. As has been stated, up to the time of delivery we were unable to find any anti-Rh substance in her serum. However, serum taken on the day of delivery, when set up against 10 different known Group O, Rh+ cells, agglutinated weakly 3 of the 10 groups of cells. The other 7 were unaffected. Subsequent examinations of the blood taken postpartum failed to substantiate these findings. We felt then, that we were dealing with an anti-Rh antibody of low titer and further since only 3 of the 10 groups of cells were agglutinated by the patient's serum, that we were not dealing with the ordinary Rh isoantibody, but rather with a subgroup of the Rh agglutinin, Rh₁ or Rh₂.⁵

We believe that this case again illustrates the efficacy of using Rh-, anti-Rh- donors in transfusing the infant suffering from one of the various forms of erythroblastosis.

Right here it would not be amiss to state that we feel the term "erythroblastosis," in naming the group of diseases from which these infants suffer is a misnomer. It implies that all infants suffering from icterus gravis, fetal hydrops, hemolytic anemia, etc. must have erythroblasts in goodly numbers in their blood streams. Actually of course this is not true, as demonstrated by 2 of our cases (4 and 6). "Hemolytic Disease of the Newborn" is more accurately descriptive of the disease since hemolysis is the basic reaction activating these clinical syndromes and is suggested as a much more desirable term than "Erythroblastosis."

CASE 6. Mrs. C., a 28 year old para ii, grava iii, Wassermann negative. In 1939 she delivered a premature infant which was otherwise normal. In 1940 the 2d pregnancy terminated at term with a normal infant. The most recent pregnancy terminated in another hospital on March 24, 1942, by low forceps delivery of a full-term normal-appearing infant. On March 25 it was noted that there was some icterus which became more marked as time went on. On March 26 the infant's blood count was: R.B.C. 3.98 million, and Hb. 10.6 gm. Bleeding and clotting time normal. On March 31 the R.B.C. count was 1.3 million and Hb. 3.9 gm. On this day a smear showed no erythroblasts. The infant was given 15 cc. of whole blood intramuscularly. On April 1 it was noted that the spleen was palpable, and the diagnosis of erythroblastosis was considered. It was excluded however, because of the absence of erythroblasts in the blood smear. Late that day the infant was given a transfusion of 75 cc. of Group A citrated blood. The infant's father was the donor. One hour later the infant died. The autopsy showed the diagnosis to be erythroblastosis fetalis.

After the diagnosis had been made we were consulted regarding Rh studies. We found the mother to be Group A, Rh-, and to have anti-Rh substance in her serum. Blood taken from the infant postmortem showed it to be Group A, Rh+.

We present this case, not as an example of poor management, but as one in which if the rôle of the Rh factor in erythroblastosis had been recognized, the end-results might have been different. The infant lived 9 days with inadequate treatment, and we believe

had it been treated according to the plan we have outlined that it would possibly be alive today. Certainly the infant should have had several transfusions, starting with the first drop in hemoglobin and R.B.C. count. And certainly these transfusions should have been from Rh—, anti-Rh— donors, and not from the Rh+ father as was done in this case.

Summary. 1. Six cases of erythroblastosis fetalis are presented in which the mother was immunized by the Rh agglutinin from the fetus.

2. In one of these cases, by means of Rh studies on the mother antepartum, the subsequent delivery of an erythroblastotic infant was expected.

3. This infant was treated by numerous transfusions of Rh—, anti-Rh— blood.

4. This line of therapy is recommended in all cases of erythroblastosis.

5. A case of "habitual aborter" is described in which the absence of the Rh factor in the mother seems to be the cause of the repeated abortions.

6. It is suggested that the term "Erythroblastosis" be dropped and the conditions ieterus glavis, fetal hydrops, hemolytic anemia, etc., be included under the term "Hemolytic Disease of the New-born."

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ABSORPTION OF SULFADIAZINE AFTER ORAL AND INTRA-PERITONEAL ADMINISTRATION IN DOGS AND AFTER INTRAPERITONEAL AND LOCAL ADMINISTRATION IN MAN

By A. M. AMBROSE, PH.D.

ASSISTANT PROFESSOR OF PHARMACOLOGY

R. ARNOLD GRISWOLD, M.D.

PROFESSOR OF SURGERY

AND

JOSEPH E. HAMILTON, M.D.

ASSISTANT PROFESSOR OF SURGERY

LOUISVILLE, KY.

(From the Department of Pharmacology and the Department of Surgery, University of Louisville School of Medicine, and Louisville General Hospital)

THE relative absorption rates of sulfanilamide, sulfathiazole and sulfaguanidine after oral and intraperitoneal administration in dogs with a discussion of their clinical significance have been previously

reported.^{1,4,11} Since the synthesis of sulfadiazine,⁹ considerable interest has been aroused in the use of this relatively new chemotherapeutic agent. Feinstone, Wolff, Huntington and Crossley,³ in studying the toxicity, absorption and chemotherapeutic effectiveness in experimental animals found the drug less toxic, caused less tissue damage than sulfapyridine or sulfathiazole and that it had a higher therapeutic activity in pneumococcal, streptococcal, staphylococcal and Group B Friedländer's bacillus infection. In man it was found that the drug is readily absorbed from the gastrointestinal tract, not so readily excreted, and that its disappearance from the blood is slower than sulfathiazole.^{7,8}

Of the more common sulfonamides in use (sulfanilamide, sulfapyridine, sulfathiazole and sulfaguanidine), sulfadiazine is the least soluble; approximately 12 mg. per 100 cc. water at 37° C. as compared to 800, 54, 96, 220 mg. per 100 cc. for each of the other sulfonamides respectively. Because of its low toxicity, superior effectiveness against pathogenic organisms and its low solubility suggested to us that sulfadiazine would be more ideally suited as an adjunct in the prevention of postoperative infection. For these various reasons, and the desire to determine the margin of safety of reinforcing the local treatment by oral administration of sulfadiazine or other sulfonamides, we have studied the absorption rate of sulfadiazine after oral and intraperitoneal administration in dogs and after intraperitoneal and local administration in man.

Experimental. In one series of experiments 4 dogs were used for each of the two methods of administration. The dose of powdered sulfadiazine was 100 mg. per kg. In order to determine the relationship between dose and blood concentration, another small series of experiments consisting of 1 dog for each of the two methods of administration was used. The dose of sulfadiazine was 500 mg. per kg. All dogs were deprived of food and water 12 hours prior to the experimental procedure and for an additional 24 hours following administration of the drug. When sulfadiazine was administered orally, it was administered suspended in water by stomach tube. For intraperitoneal administration, surgery was performed under ether anesthesia. A midline abdominal incision was made, powdered sulfadiazine was applied to the intestines directly beneath the greater omentum, and the incision closed with catgut and silk. For the purpose of determining the extent of absorption, blood was taken at hourly intervals for the first 7 or 8 hours following administration, and at 24-hour intervals thereafter until the test was negative.

In 7 patients subjected to abdominal surgery under spinal or cyclopropane-ether anesthesia, 5 gm. of powdered sulfadiazine were placed within the peritoneum, the abdomen was closed without drainage, and absorption of the drug was followed every 2 hours during the first 24 hours following administration, every 6 hours for the following 24 hours, every 12 hours for the next 24 hours, and every 24 hours thereafter until the test became negative, or the patient was discharged from the hospital. The values were not followed to zero, as we were concerned with the chief extent and rate of absorption rather than the end-point. Urinary excretion was followed every 24 hours whenever possible. In 1 patient operated upon for an aneurysm of the right femoral artery, another for stab wound of the chest, and a third for incarcerated hernia, 5 gm. of powdered sulfadiazine were placed in the operative field, incision closed without drainage and absorp-

tion of the drug was followed as above. In 5 other patients, treated for second and third degree burns involving approximately 35% to 60% of the body surface, a spray containing 3% sulfadiazine in 8% trichloroamine was used, as recommended by Pickrell.⁶ In all these cases, as well as others, intravenous glucose as well as other forms of supportive therapy were administered whenever indicated. Absorption of sulfadiazine was followed at frequent intervals.

Blood concentrations and urinary excretions were determined by a modification of the method described by Bratton and Marshall² for sulfanilamide. Colorimetric comparisons were made with a Klett-Summerson photoelectric colorimeter with light filter No. 540.

TABLE 1.—COMPARATIVE ABSORPTION RATE OF SULFADIAZINE AFTER ORAL AND INTRAPERITONEAL ADMINISTRATION IN DOGS

Method of administration	No. of animals	Dose (mg./kg.)	Blood concentration—hours after administration (mg. per 100 cc.)															
			1	2	3	4	5	6	7	8	24	48	72	96	120	144	168	192
Oral	4*	100	1.6	2.2	2.7	2.8	2.8	2.8	2.7		0.8	0.2						
	1	500	4.2	6.4	6.4	6.3	5.9	5.9	5.7	5.5	1.3	0.4						
Intra-peritoneal	4*	100	2.0	3.0	3.6	3.7	3.5	3.3	3.2		2.4	1.5	0.7	0.5	0.5	0.4	Tr.	Tr.
	1	500	3.1	6.3	7.2	7.7	8.4	9.3	10.8	13.8	25.3	19.9	16.1	10.1	4.4	2.4	1.3	0.8

* Average.

Tr. = Tracc.

Results. From the average blood levels for each of the two methods of administration after 100 and 500 mg. per kg., it is seen (Table 1) that sulfadiazine is rapidly absorbed from both the gastrointestinal tract and peritoneum, the peak being reached in 3 to 4 hours after administration; with the exception of 1 dog receiving 500 mg. per kg. intraperitoneally, the peak concentration was not reached until sometime between the 8th and 24th hour after administration. After oral administration of 100 or 500 mg. per kg. the rate of disappearance from the blood is the same as that reported by Feinstone *et al.*,³ and the same as that for sulfanilamide,⁴ sulfathiazole¹¹ and sulfaguanidine.¹ However, after intraperitoneal administration of 100 mg. per kg. the rate of disappearance from blood is considerably slower than for other sulfonamides studied under similar conditions. Approximately 0.4 mg. % sulfadiazine was present in the blood after 144 hours as compared to only traces of the other sulfonamides after 48 hours.

In Table 2 are tabulated results on 3 human subjects in which sulfadiazine was placed within the peritoneal cavity. Results on the other patients are much like those presented, excepting that in a few patients procaine was used as the anesthetic (which interferes with the determination of sulfonamides) and in others urinary excretion studies were not as complete as those presented. We have purposely selected 3 cases receiving the drug intraperitoneally and 2 receiving the drug cutaneously, of the total studied, as being repre-

sentative, rather than give all our data as we felt that this would be more repetitious than valuable. As can be seen from the table the rate of absorption from the human peritoneum is quite different from that observed in dogs. As to why there should be a difference in rate of absorption, we have no explanation to offer other than possibly the conditions in dogs were not comparable to those in man.

TABLE 2.—FATE OF A SINGLE INTRAPERITONEAL DOSE (5 GM.) OF SULFADIAZINE IN MAN

Patient	Hours after admin.	Sulfadiazine concentration						
		Blood (mg. per 100 cc.)		Urine excretion				
		Free	Total	Vol. cc.	Free mg.	Total mg.	% conjugated	% of total cumulative
1 D. M.	2	0 7						
	5	0 9						
	14	1 3	1 3					
	39	1 4	..	780	151	632	76	12 6
	45	1 7						
	59	2 6						
	72	2 7		910	483	697	31	26 6
	96	2 7	.	860	613	844	17	43 5
	108	3 2	3 3					
	120	2 2	..	910	977	1310	25	69 6
	144	0 9	.	910	311	369	16	77 0
	168	0 7	.	912	127	176	28	80 6
	192	0 5	.	795	107	124	9	85 0
	216	0 3	.	1500	77	94	17	87 0
2 W. S.	2	3 8	4 2					
	4	2 8	2 8					
	6	2 6	2 7					
	12	2 5	2 5					
	24	2 4	.	690	1292	1750	26	35 0
	48	1 8	1 8	680	655	960	32	54 2
	72	1 5	1 5	225	132	237	44	58 9
	96	1 1	.	630	276	546	49	69 9
	120	0 9	.	670	193	344	41	76 7
	144	0 8	.	760	138	212	35	80 9
	168	0 8	.	1030	154	198	22	84 9
	192	0 8	.	590	101	145	30	87 8
	216	0 7	0 7	730	117	187	37	91 6
	240	0 6	0 7	460	69	113	40	93 8
	264	0 7	.	310	53	54	2	94 9
3 J. B.	288	0 5	0 6	460	23	25	..	95 4
	456	0 3	0 3					
	3	1 8						
	9	1 9						
	12	1 6						
	24	0 9	0 9	850	282	284	..	5 7
	43	0 8	0 8	660	99	99	..	7 7
	69	0 7	..	320	44	45	..	8 5
	93	0 9	0 9	150	29	37	22	9 3
	117	0 9						
	165	0 6		730	87	117	26	11 6
	189	0 8	0 8	860	119	174	31	15 1
	213	0 6	.	680	94	156	40	18 2
	261	0 6	.	720	194	276	30	23 8
	333	0 8	0 8	800	266	419	36	32 1
	357	0 8		270	95	133	29	34 8
	381	0 8	0 8	180	59	90	34	36 6
	453	0 8	.	536	166	297	44	42 5
	572	0 6	0 6	1145	271	436	36	51 3

While others have reported peak blood concentrations of approximately 8 mg. per 100 cc. in 4 to 8 hours after oral administration,^{5,10} and approximately 10 mg. per 100 cc. in 2 to 3 hours after subcutaneous administration of 5 gm. of sulfadiazine,¹¹ in our experiments maximum blood concentrations were reached in 2 to 108 hours after administration and this rarely exceeded 4 mg. per 100 cc. The rate of disappearance of sulfadiazine from blood, after interperitoneal administration, is also considerably slower than that reported by others by different routes of administration.^{5,7,10} For the most part blood concentrations of approximately 1 mg. per 100 cc. were maintained for about 144 hours. Traces of the drug were still present 216 to 572 hours after administration. The presence of conjugated sulfadiazine in the blood was found only occasionally, and this rarely exceeded 5% of the free drug. This is substantially in agreement with that reported by others after oral and subcutaneous administration.^{5,7,10} Urinary excretion of the drug was followed in 3 patients. In 1 patient 85% of the drug was excreted within 216 hours, in the second 95% within 288 hours, and in the third 51% within 572 hours. This is considerably slower than that reported by Satterthwaite *et al.*,¹⁰ in which they find practically all of the drug excreted within 36 to 48 hours after oral administration, and by Peterson *et al.*,⁵ in which they report recoveries of 62% to 92% of the drug within 72 hours after oral, intravenous or subcutaneous administration.

TABLE 3.—ABSORPTION OF SULFADIAZINE AFTER CUTANEOUS APPLICATION IN MAN

Patient	Hours after admin.	Sulfadiazine concentration					
		Blood (mg. per 100 cc.)		Urine excretion			
		Free	Total	Vol. cc.	Free mg.	Total mg.	% conjugated
G. P.	6	4 8	5 2				
	12	7 3	8 4				
	24	12 1	13 3				
	36	12 8	13 2				
	48	11 6	11 9	1850	1884	3345	44
	60	7 9	7 9				
	72	4 4	4 4	210	447	602	25
	84	2 4	2 4				
	96	2 5	2 5	1100	2801	3507	20
	120	2 7					
M. M.	8	5 5	5 5				
	14	7 0	7 1	130	25	39	36
	19	6 2	6 5	150	157	300	48
	29	7 5	8 1	95	124	228	45
	44	9 1	10 4	70	91	192	52
	67	9 5	10 3	430	635	1242	49
	90	8 2	9 1	800	890	1729	48

In the patients in which powdered sulfadiazine was placed within the operative field as well as in the incision, absorption and excretion was even slower than that observed from the peritoneum.

Blood concentrations ranging between 0.8 and 1.33 mg. per 100 cc. were maintained for more than 250 hours after administration. Total urinary excretion in 1 patient who was kept under observation longer than others (312 hours) was 41% of the drug administered.

In Table 3 are recorded the results on 2 patients treated for burns with "sulfadiazine spray." In other patients similarly treated the results were essentially the same, with the exception of 1 patient who will be discussed separately. As can be seen from the table, absorption during the first 90 hours of treatment is considerably more rapid and greater than absorption from the peritoneum or from surgical wounds. Blood concentrations during this period of observation more closely approximated those reported by Peterson *et al.* after oral or subcutaneous administration of sulfadiazine. In the 1 patient treated in which the burned area involved approximately 60% of the body surface, blood concentrations as high as 30 mg. per 100 cc. were obtained. Four hours before death the blood concentration had fallen to 23 mg. per 100 cc. Throughout the course of treatment (96 hours) the patient remained incontinent. About 50 cc. of urine was obtained by catheterization shortly before death. Sulfadiazine concentration of this specimen was 6 mg. per 100 cc. Microscopic examination for free and conjugated sulfadiazine was negative. The remaining 4 cases also terminated fatally. Death was probably due to secondary infection or pneumonia. Autopsy in all of these patients was refused.

One striking difference observed in these patients and those receiving the drug intraperitoneally or in surgical wounds was the amount of conjugated drug in the blood. In comparing these results with those obtained after intraperitoneal administration, it is quite apparent that conjugation occurred more frequently, although the amount of conjugated sulfadiazine in the blood seldom exceeded 10% of the total blood concentration.

Microscopic examination for free and conjugated sulfadiazine was made on all urine collected. In the 1 dog receiving 500 mg. per kg. intraperitoneally, crystals of free sulfadiazine were found in all urine voided over 120 hours. In all other dogs no crystals of the free drug were found in the urine. In human subjects crystals of free and conjugated sulfadiazine were found only in the urine of patients receiving sulfadiazine cutaneously, with the exception of the 1 patient previously discussed.

In examining all our data on urinary volume and excretion we find that precipitation of free or conjugated sulfadiazine occurred only when blood concentrations were high or urine volumes low. In urinary concentrations below 180 mg. per 100 cc. total sulfadiazine, no crystallization of free or conjugated drug occurred. However, when urinary concentrations exceeded 180 mg. per 100 cc., crystallization of the free or conjugated drug invariably occurred.

This was particularly true in the 1 dog receiving the large dose of sulfadiazine intraperitoneally, and in patients, during the first few days of treatment, receiving sulfadiazine sprayed cutaneously on burned areas.

Discussion and Summary. In man sulfadiazine has been reported⁵ as being rapidly absorbed after oral or subcutaneous administration of a single dose of 5 gm. and that higher blood concentrations are reached, sustained longer, and excreted more slowly than with similar doses of sulfanilamide, sulfapyridine or sulfathiazole. Our experiments on dogs, after oral administration of 100 mg. per kg., indicate a degree of absorption less than that reported for sulfanilamide,⁴ sulfathiazole,¹¹ or sulfaguanidine,¹ and its disappearance from blood approximately that of these sulfonamides. After intraperitoneal administration of 100 mg. per kg. in dogs, the peak concentration is less than that reported for sulfanilamide,⁴ and intermediate between that reported for sulfathiazole¹¹ and sulfaguanidine.¹ However, peak concentrations are maintained longer with traces of the drug still present after 192 hours as compared to 48 hours for other sulfonamides similarly administered.

In man appreciable absorption of sulfadiazine is still evident 216 to 572 hours after intraperitoneal or local administration, as compared to only traces of the drug 48 hours after oral or subcutaneous administration of a single dose of 5 gm.⁵ After cutaneous application of sulfadiazine spray on burns, absorption is more rapid and blood concentrations higher than those observed after intraperitoneal administration or local application in wounds. This is particularly evident during the first 90 hours of treatment after which blood concentrations rapidly fall to approximately 2 mg. per 100 cc., at which level they remain even though spraying was only continued occasionally.

These experiments suggest that sulfadiazine intraperitoneally is more ideally suited to be a prophylactic agent in the prevention of postoperative infection than other sulfonamides, since it is more slowly absorbed, so that more of the drug remains *in situ* to produce a more lasting bacteriostatic effect. These results also suggest that reinforcing the local treatment with oral administration of sulfadiazine or other sulfonamides whenever indicated may well be undertaken, particularly in patients where sulfadiazine is used within the abdominal cavity or in wounds, provided the usual precautions for these drugs are followed.

We are indebted to Drs. A. D. Welch and Earl L. Burbidge, Sharp & Dohme, Inc., Philadelphia, Pa., for the powdered sulfadiazine, and to the Lederle Laboratories, Pearl River, N. Y., for solutions of sulfadiazine used in this study.

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PREVENTION OF INFECTIOUS ULCERATIVE CECITIS IN THE YOUNG OF RATS BY CHEMOTHERAPY OF THE MOTHER

By ARTHUR L. BLOOMFIELD, M.D.

PROFESSOR OF MEDICINE

AND

WILLIAM LEW

LABORATORY ASSISTANT

SAN FRANCISCO, CAL.

(From the Department of Medicine, Stanford University School of Medicine)

In a previous paper we demonstrated the prophylactic effect of sulfaguanidine against ulcerative cecitis of the rat.¹ Briefly, if 0.5% sulfaguanidine were mixed with the stock diet, animals sacrificed after 82 days were only occasionally affected, whereas most of the controls showed advanced disease. We, as well as others,² have described the course of the lesions. Suffice it to say here that the earliest change is a tiny superficial ulceration of the cecal mucosa. This gradually enlarges to reach immense proportions (2 to 3 cm.) with thickening of the bowel wall and extensive pericecal adenitis and cystlike pockets of clear fluid. In extreme cases there is a mass the size of a walnut made up of glands, cysts and matted coils of intestine. The cause of this interesting disease is not yet established. Buchbinder and his associates³ feel it is a paratyphoid bacillus infection. We have confirmed the frequency of *Salmonella enteritidis* in the cecal contents and in regional nodes, but the exact significance of these organisms is not yet clear.²

Be this as it may, Buchbinder³ found that rats removed at weaning from further contact with the mothers were not likely to develop cecitis, whereas those left with their dams later showed evidence of infection. It seemed of interest therefore to find out if sulfaguanidine added to the diet of the mother would confer any protection on the young. At the time of these experiments cecitis was actively epidemic in the rat colony. Healthy stock animals up to the age of 3 or 4 months rarely showed any definite lesions, but from 5 months on cecitis was frequent and the majority of the older animals, of 8 months or over, had advanced forms of the disease. The exact mode of dissemination of the infection has not yet been

worked out but there must have been a continuous contamination of the animals' quarters so that the agent is introduced with food, handling, during sweeping of quarters, cleaning of cages, etc. Hence any group of rats even if they were placed from the time of weaning in a separate cage eventually developed cecitis. We have no observations on young which have been isolated in the bacteriologic sense.

Inasmuch as cecitis may progress slowly over a period of months, it is evident that in the experiments to be described below one must consider not only the incidence of the disease in an experimental group of rats but also the degree of the lesions. These were carefully graded according to the following scale:

- 0 = no cecitis
- + = superficial erosion not over 0.5 cm. in diameter
- ++ = ulcer 0.5 to 1 cm. in diameter with greenish slough and pericecal adenitis
- +++ = ulcer over 1 cm. in diameter with thickening of cecal wall and marked pericecitis
- ++++ = extreme lesions with huge ulcer and matted adherent coils of intestine

On this basis a percentage figure for degree of infection could be calculated. If 4+ indicates the most advanced lesion, then $4 \times$ the number of rats would equal 100% of the maximum possible degree of infection in the group. This figure divided into the sum of the observed pluses gives the percentage intensity of the lesions in the experimental group. We are aware of all the errors of such a method of calculation but figures arrived at in this way are necessary to supplement those dealing with the mere incidence of the disease.

Experiments. *Experiment 1.* A series of healthy females about 3 months old were given the stock laboratory diet to which 0.5% of sulfaguanidine was added. The animals were then placed with healthy males of about 4 months and the sulfaguanidine ration was continued throughout pregnancy and until the young were weaned. After weaning, one-half of the rats continued to receive sulfaguanidine rations, whereas the other half were kept on the same stock diet but without the drug. The rats were weaned on June 2, 1941, and sacrificed on December 19, 1941. Along with the two sets of rats described above, a series of controls was run as follows: Control mothers were bred at the same time as the mothers on sulfaguanidine and the offspring were weaned at approximately the same time. They were treated just like the experimental animals and were killed on the same day. The only difference was that neither the controls nor their mothers at any time received sulfaguanidine.

The results can be briefly summarized as follows:

TABLE 1—SUMMARY OF EXPERIMENT 1

	Group		
	A	B	C
Mother during pregnancy . . .	On sulfaguanidine	On sulfaguanidine	No sulfaguanidine
Mother during nursing period . . .	On sulfaguanidine	On sulfaguanidine	No sulfaguanidine
Young after weaning and throughout experiments . . .	On sulfaguanidine	No sulfaguanidine	No sulfaguanidine
Incidence of cecal disease when young were sacrificed 6½ months after weaning	None	None	83% advanced lesions for the most part

TABLE 2.—DATA ON RATS OF GROUP C

Lab. No. mother	Lab. No. young	Birth- day of young	Weight at weaning (gm.)	Age at weaning (days)	Weight when sacrificed (12/19/41) (gm.)	Cecitis at autopsy	
						Description	Grade
51895	36	5/8/41	30	23	276	None	0
	37	..	34	23	268	No ulcer, but huge glands	+
	38	..	32	23	240	Ulcer 1 cm., whole cecum indurated, large glands and cysts	+++
	39	..	32	23	242	Ulcer 0.8 cm., large glands and cysts	++
	41	..	34	23	254	No ulcer, but huge glands all through mesentery	+
51925	66	5/12/41	22	23	248	Ulcer 1 cm., whole cecum scarred, large glands and cysts	+++
	67	..	22	23	190	Ulcer 1 cm., whole cecum scarred, large glands and cysts	+++
	68	..	22	23	220	Ulcer 0.8 cm., large glands and cysts	++
51940	79	5/12/41	20	23	174	Huge ulcer, whole cecum indurated and matted with huge glands and cysts	++++
	80		21	23	210	Huge ulcer, whole cecum indurated and matted with huge glands and cysts	++++
	81	..	22	23	194	None	0
	82	..	21	23	210	Ulcer 2 cm., whole cecum indurated, huge glands and cysts	++++
				av. 26		av. 227	

TABLE 3.—SUMMARY OF EXPERIMENT 2

	Group		
	A	B	C
Number of rats	18	19	33
Mothers during pregnancy	On sulfa- guanidine	On sulfa- guanidine	No sulfa- guanidine
Mothers during nursing period	On sulfa- guanidine	On sulfa- guanidine	No sulfa- guanidine
Young after weaning	On sulfa- guanidine	No sulfa- guanidine	No sulfa- guanidine
Incidence of cecitis when young were sacrificed (% of group affected)	None = 0	2 = 10%	18 = 54%
"Degree" of cecitis (%)	0	4	28

CHART 1.—DEGREE OF LESIONS IN EXPERIMENT 2

[illegible]

Each vertical row indicates the degree of the lesion in 1 animal.

From our previous experience it was to be expected that the rats which were on sulfaguanidine rations throughout life would not have cecitis. It was equally certain that many of the controls would show advanced lesions. The complete absence of cecitis in the rats whose mothers had received the drug (Group B) but who themselves never had any was not anticipated and it was clear that such a striking result required further confirmation. This was obtained in the following experiments, and a discussion of possible explanations will also be given. It may be said at this point, however, that the results were not due to accidental selection of resistant animals. This is ruled out by the large number of mothers (6 in Group A, 5 in Group B) selected at random from the same stock as the 3 control mothers of Group C. Groups A and B showed no positive findings at autopsy. The detailed findings in the positive group (C) are shown in Table 4.

Experiment 4. This experiment was planned to discover if treatment of the mother with sulfaguanidine during pregnancy or lactation only conferred any protection. Seventeen young of mothers who received sulfaguanidine during pregnancy only, and 25 young of mothers who received sulfaguanidine in lactation only, were followed just as in Experiments 1 and 2. When sacrificed after 5½ months none of these animals had cecitis as against an incidence of 54 % in the control young of mothers who received sulfaguanidine.

Finally, Table 5 gives a summary of all the experiments.*

TABLE 5.—SUMMARY OF ALL EXPERIMENTS

	Cecitis			% incidence	% severity
	No.	Present	Absent		
All controls (no sulfaguanidine in mothers or young)	65	48	17	74	41
All young of mothers receiving sulfaguanidine during pregnancy and/or lactation	69	2	67	3	1
Sulfaguanidine to mother and young throughout experiment	26	0	26	0	0
Young pregnant with:	17	9	8	52	19

Discussion. The general results of these experiments seem quite definite: the young of mothers who receive sulfaguanidine during pregnancy and lactation develop ulcerative cecitis much less frequently and in milder form than control animals from untreated mothers. This "resistance" is manifest even when test animals are raised in the same cages with highly diseased rats, although under these circumstances the incidence and degree of cecitis is greater. Furthermore, sulfaguanidine given to the mother during either pregnancy or lactation seemed to result in resistance on the part of the young.

We have as yet no exact explanation of these interesting phenomena. It must be recalled that the etiologic agent of rat cecitis is unknown. *Salmonella* are, to be sure, frequently present in sick animals, but we have strong evidence against these being the primary cause of the disease.² The possibility of some other category of infectious agent such as a virus is by no means ruled out. It is also to be noted that practically all the rats in an infected colony were perfectly well for the first 2 or 3 months; during this time no lesions were visible but we are not by any means sure that infection did not already exist. With viruses in particular, long latent periods are known to occur as, for example, with rabies and with herpes;⁵ some of the natural viruses of mice and rabbits may apparently be carried indefinitely without producing evident disease.⁴ Still other viruses persist in the host after recovery from clinical infection.⁹ Finally, a virus may be carried by a host without producing disease until "activated" by some other agent.⁶ The rôle of *Hemophilus influenzae suis* in activating the virus of swine influenza,

* Dr. Charles W. Barnett analyzed the figures and showed that the differences in incidence of cecitis in test and in control animals are statistically valid.

which may lie dormant for at least 2 years in the swine lungworm, has been convincingly demonstrated by Shope.⁷

It may be, then, that the unknown infectious agent of rat cecitis is usually acquired very early in life; it is possible that destruction or inhibition of this agent in the mother by means of chemotherapy allows the young to escape invasion at a vulnerable period of life. Disease, if it occurred at all in these animals, would then be acquired later and perhaps only from a heavy exposure, as in Experiment 3. It is even possible that the *Salmonella* which are so constantly present in cecitis may serve to activate a virus which otherwise lies dormant in the infected rat. But speculation seems unprofitable until the causal organism is definitely identified and the usual mode of invasion is worked out. Meanwhile these experiments are put on record because they represent a new type of procedure in practical chemotherapy.

Conclusions. 1. The young of rats which receive 0.5% of sulfaguanidine in their food during pregnancy and lactation only occasionally developed ulcerative cecitis, whereas 74% of the young of untreated mothers acquired the disease.

2. Young of treated mothers raised in the same cages with young of untreated mothers developed cecitis much more frequently than if segregated, but a high degree of resistance is still demonstrable.

3. Administration of sulfaguanidine to the mothers during either pregnancy or lactation seems to confer resistance to cecitis on the young.

4. Possible explanations of this phenomenon are discussed.

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CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS IN SEVERE EPILEPSY UNDER TREATMENT

By DOUGLAS GOLDMAN, M.D.

CLINICAL DIRECTOR, LONGVIEW HOSPITAL
CINCINNATI, OHIO

(From Longview State Hospital)

THE last decade has seen remarkable advances in the diagnosis and treatment of convulsive disorders. Diagnosis has become more certain and satisfactory with the help of the electroencephalograph

(E.E.G.)¹ and the introduction of diphenylhydantoin^{2,3} in therapy has been a means of bringing relief to many patients resistant to previously available medication.

This report is the result of study of a group of severe epileptics over a long period with aid of the E.E.G., while determining the effects of medication, chiefly dilantin sodium and phenobarbital. Most of the patients were psychotic inmates of a State mental hospital whose psychoses were a manifestation of convulsive disorder. As a group these patients were examples of the most severe type of chronic, long-standing illness. A few private patients of particular interest are included in the series. It is believed that patients with severe illness serve best to indicate the true worth of any form of treatment, particularly when purely clinical evidence can be supplemented with objective data such as that furnished by the E.E.G.

The patients are grouped according to severity as indicated in Table 1. Brief protocols of individual patients serve as legends for the tracings made at appropriate intervals during observation. The tracings of all but the *petit mal* patients were made in intervals between seizures.

TABLE 1.—SEVERITY OF SEIZURES

No.	Duration of convulsive disorder	Age Sex	Before treatment	After treatment	Treatment	Time observed	Result	
							Clinical	E.E.G.
1	Over 30 yrs.	66 F	4	3	Dilantin Phenob.	3 yrs.	Fair	Fair
2	Over 30 yrs.	46 F	4	3	Dilantin	3 yrs.	Fair	Fair
3	Over 20 yrs.	64 M	4	3	Dilantin	3 yrs.	Good	Fair or +
4	About 19 yrs.	32 M	4	3	Dilantin	3 yrs.	Good	Fair
5	Over 50 yrs.	62 M	4	3	Dilantin Phenob.	3 yrs.	Fair	Fair
6	About 2 yrs.	20 M	4	3-4	Dilantin	2 mos.	Fair	Good
7	About 23 yrs.	44 F	3	2	Dilantin	18 mos.	Good	Good
8	6 yrs.	25 F	4	2	Phenob.	2½ yrs.	Good	Good
9	10 yrs. ±, no g.in.	42 M	3	1	Dilantin	3 yrs.	Good	Good
10	3 yrs.	12 F	3	1-2	Dilantin Phenob.	15 mos.	Good	Good
11	1 year ±	38 F	3	1-2	Dilantin Phenob.	9 mos.	Good	Good
12	20 yrs. ±	42 M	3	1	Dilantin	2 yrs.	Excellent	Excellent
13	6 mos.	2 M	2	1	Dilantin	1 yr.	Excellent	Excellent
14	6 mos.	5 F	3	1	Dilantin Phenob.	3 yrs.	Excellent	Excellent
15	1 year ±	18 M	3	1	Dilantin	2 yrs. +	Excellent	Excellent
16	? yrs.	25 F	3	1	Dilantin	2 yrs.	Excellent	Excellent

Grade 1—Complete absence of seizures or equivalents over 6 months.

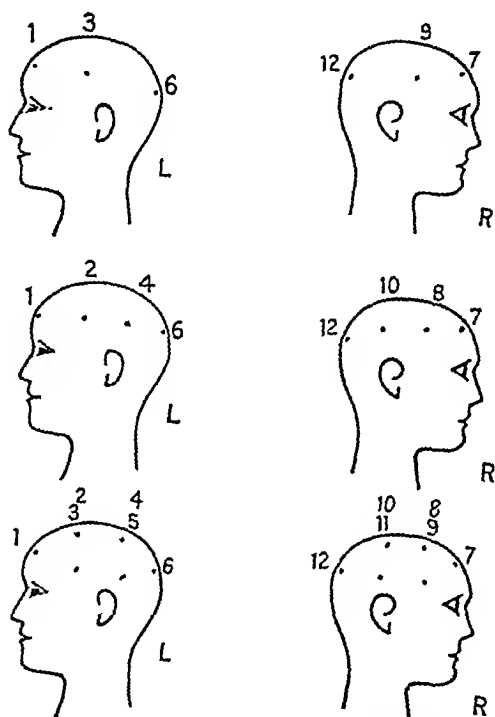
2—Seizures or equivalents not oftener than once monthly.

3—Seizures or equivalents not oftener than once weekly.

4—Seizures or equivalents more often than weekly. Most of these patients had multiple daily attacks at times.

All of the patients of Grade 4 severity were old inmates, typical cases of severe psychosis with epilepsy of long duration. Such cases are usually considered unworthy of any therapeutic effort, yet everyone of these patients received some benefit from continued treatment. Restraint became only an occasional expedient instead of a more or less constant necessity. Patients Nos. 3 and 4 are now able to help with some ward tasks. Patient No. 5 had frequent bouts of cardiac decompensation associated with frequent seizures. With reduction in number of seizures cardiac function has been

adequate. Patients Nos. 1 and 2 are much less belligerent and aggressive and no longer have injuries resulting from violent collision with the environment during seizures. All of these (Grade 4) patients are still psychotic and require hospital care, but the benefit of treatment is not to be scorned because it falls short of complete relief. Grade 3 patients are in many respects as severe as those of Grade 4 but showed better response to treatment. Patients 7 and 8 have been able to return home with their families. Patient 8 suffered one relapse when treatment was neglected by a rather feeble-minded husband; she returned to at least an equally improved level after renewed treatment. Among the Grade 2



Key to electrode location in Figures 1 to 16

patients, No. 9 is an interesting example of psychomotor epilepsy which would not have been recognized without the E.E.G. While taking dilantin his conduct is exemplary and he has suffered but one temporary relapse when treatment was omitted. The Grade 1 patients are living answers to sterile therapeutic skepticism. These are patients who have had no manifestations of epilepsy for long periods and who by their performance and behavior give unqualified evidence of recovery. Patient 12 had frequent seizures and equivalents for 20 years and has now been free for 18 months and has been gainfully employed. Patient 16 probably would not have required State Hospital care had treatment been instituted at an earlier date.

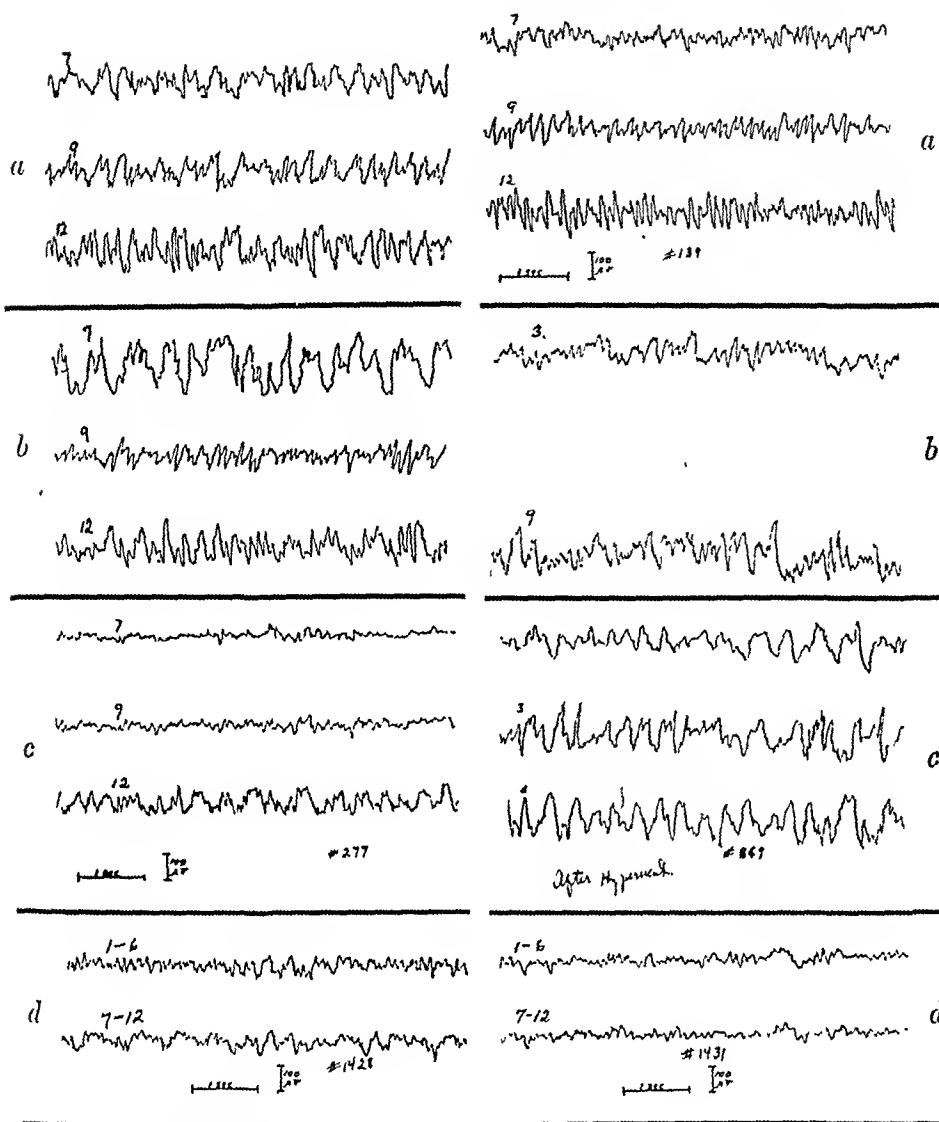


FIG. 1

FIG. 2

FIG. 1.—Patient (admitted to Longview Hospital in 1915; age 31) had had seizures for many years. *a*, April 6, 1939, seizures oftener than once daily, confused and belligerent. No treatment. Typical epileptic tracing. *b*, May 22, 1939, another control tracing, no treatment being given. *c*, June 29, 1939, having dilantin, 3 grains t.i.d. for 9 days. Seizures less than 1 per week. Patient much more manageable but still psychotic. *d*, February 27, 1942, seizures only occasionally, less than once a week, receiving no dilantin but receiving phenobarbital, $1\frac{1}{2}$ grains, twice daily. Tracing shows some degree of improvement.

FIG. 2.—Patient (admitted to Longview Hospital in 1928; age 34) had seizures since age 13—psychosis with epilepsy. She was having seizures more frequently than once a week. Her history recounted numerous burns, fractures and other injuries resulting from seizures. *a*, April 11, 1939, control tracing without treatment, markedly pathologic E.E.G. *b*, January 17, 1940, dilantin, $1\frac{1}{2}$ grains t.i.d., for 7 weeks. Seizures less than 1 in 2 weeks. *c*, May 28, 1940, dilantin, $1\frac{1}{2}$ grains t.i.d., for 1 week. Phenobarbital, $1\frac{1}{2}$ grains b.i.d., for 2 months. Two seizures were recorded on this day and 2 on the following day. This and the preceding tracing show no diminution in pathologic activity. *d*, February 28, 1942, dilantin, $1\frac{1}{2}$ grains b.i.d., for 6 months or longer. *Grand mal* seizures only every 2 or 3 weeks and these are nocturnal. The intervals between the seizures showed the patient markedly improved in behavior although still psychotic. Tracing shows marked improvement.

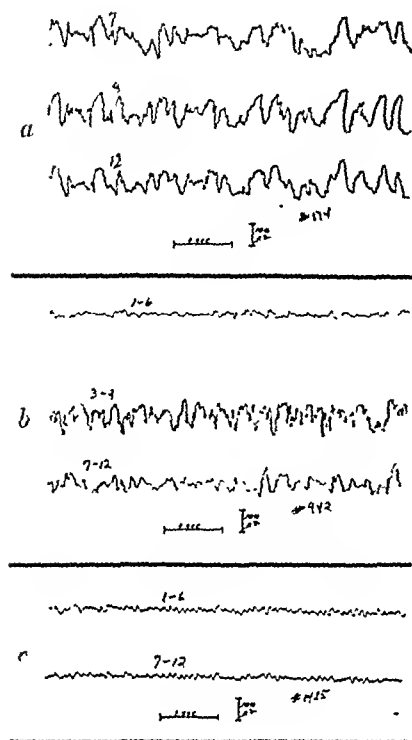


FIG. 3

FIG. 3.—Patient (admitted to Longview Hospital in 1934). Seizures since 1920 at the age of 42. Patient was confused, had frequent hallucinations, and seizures occurred about once per month or oftener. *a*, May 1, 1939, control tracing. Marked pathologic activity in E.E.G. between seizures. *b*, July 24, 1940, receiving dilantin, 1½ grains b.i.d. Seizures much less frequent but occurred every 2 or 3 months. He was able to be a ward worker, although at times his psychotic behavior was aggravated. *c*, February 26, 1942, dilantin, 1½ grains, twice daily for a year or more. Much improved, seizures occurred less often than every 2 months. He showed much less confusion and continued as a ward worker. At times psychomotor equivalents seem to replace the seizures. E.E.G. practically normal.

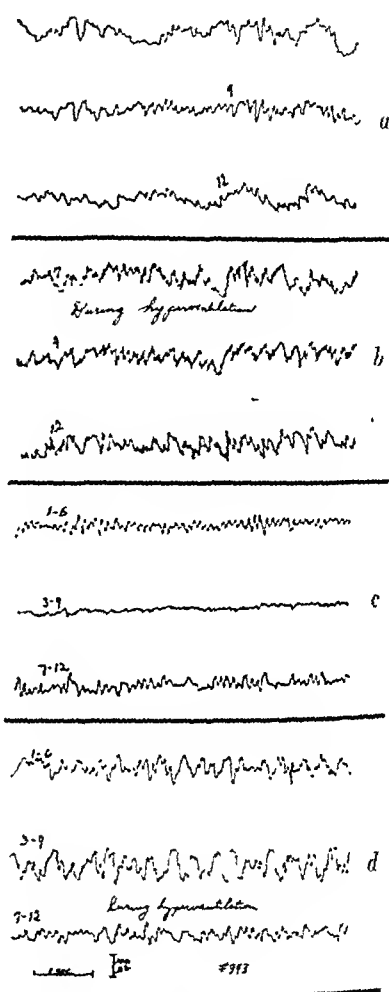


FIG. 4

FIG. 4.—Patient (admitted to Longview Hospital in 1933; age 23) had had seizures since age 14. Onset of psychosis only a few weeks before admission. Chief symptoms "organic confusion" and seizures one or more weekly, at times 2 or 3 on 1 day. *a* and *b*, Portions of control tracing—March 31, 1939. Marked pathologic activity between seizures. *c* and *d*, July 24, 1940. Patient receiving 3 grains of dilantin twice daily for over a year. He was confused and somewhat disturbed on the day of the tracing. He was having seizures at much longer intervals, once a month approximately. He was much more amenable to ordinary ward care at this time and at times served as a ward worker. E.E.G. improvement is only moderate.

In every instance without exception, as indicated in the protocols which accompany the E.E.G., the tracing parallels clinical evidence.

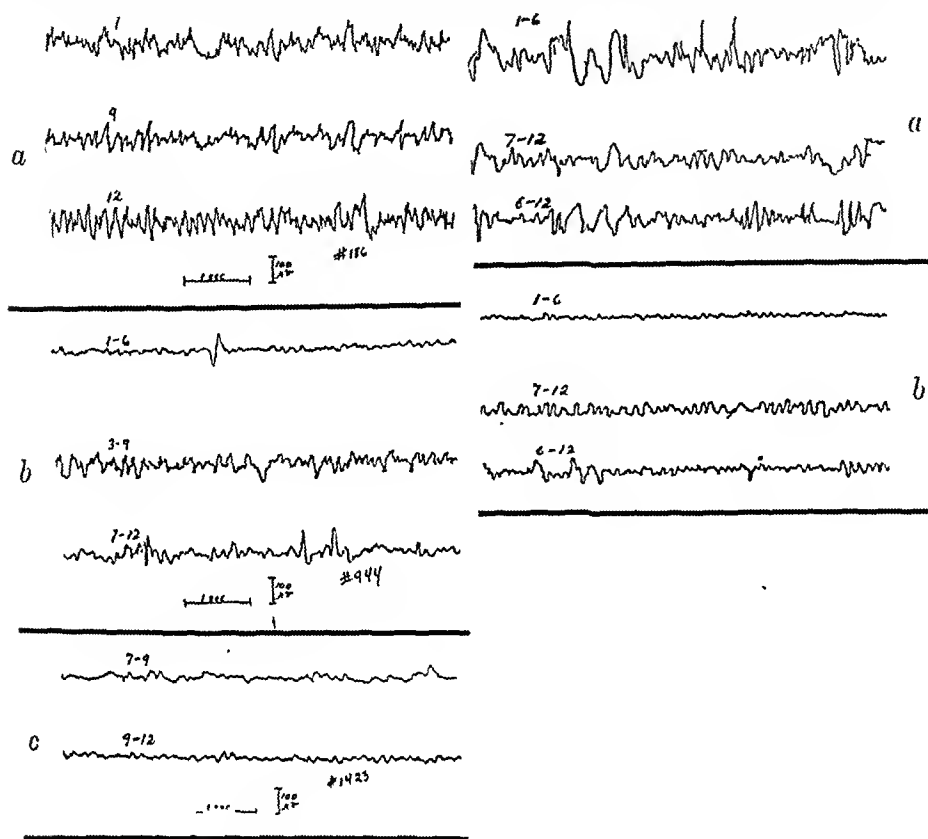


FIG. 5

FIG. 6

FIG. 5.—Patient (readmitted to Longview Hospital in 1928; age 48) had been in one or another state hospital since 1907. First seizure occurred at the age of 4 and the history relates frequent fractures and other injuries during seizures. *a*, May 9, 1939, seizures at variable intervals, sometimes daily. E.E.G. shows marked irregular pathologic activity between seizures. *b*, July 29, 1940, dilantin, $1\frac{1}{2}$ grains twice daily, for several months plus phenobarbital $1\frac{1}{2}$ grains twice daily for the last 5 months. He was suffering from cardiac decompensation and was confused and aggressive. Tracing shows only occasional slow waves and "spikes." *c*, February 25, 1942, dilantin, $1\frac{1}{2}$ grains twice daily, steadily for the last 10 months. He was having seizures once monthly or less and none for several weeks before the tracing. He was psychotic and had occasional confused and aggressive spells. Cardiac status was much improved while he was not having seizures. Tracing much more normal than clinical condition of patient would indicate.

FIG. 6.—Patient (admitted to Longview Hospital, July, 1941; age 20) had had seizures since December, 1940. Was extremely violent, tore his clothing, assaulted those around him and had a self-inflicted fracture of a metacarpal bone from striking a heavy screen with his hand. He was practically uncontrollable without restraint. *a*, July 10, 1941, control tracing. Had had sodium amytal, $7\frac{1}{2}$ grains, intravenously 2 days before. Marked irregular pathologic activity in E.E.G. *b*, July 29, 1941. Had had dilantin, $1\frac{1}{2}$ grains t.i.d., for 2 weeks. He improved remarkably at this time, clinically as well as in the E.E.G. but later seemed to become resistant to treatment which may have been inadequate and was sent to another state hospital.

Improvement or lack of it is readily recognizable from the tracings. The degree of change in the tracings was greater than might have been expected from previous reports based on shorter periods of

observation. Tracings even from the Group 3 and 4 patients showed marked change approaching normal; and those from Group 1 patients became undistinguishable from normal. (Group number refers to grade of result.)

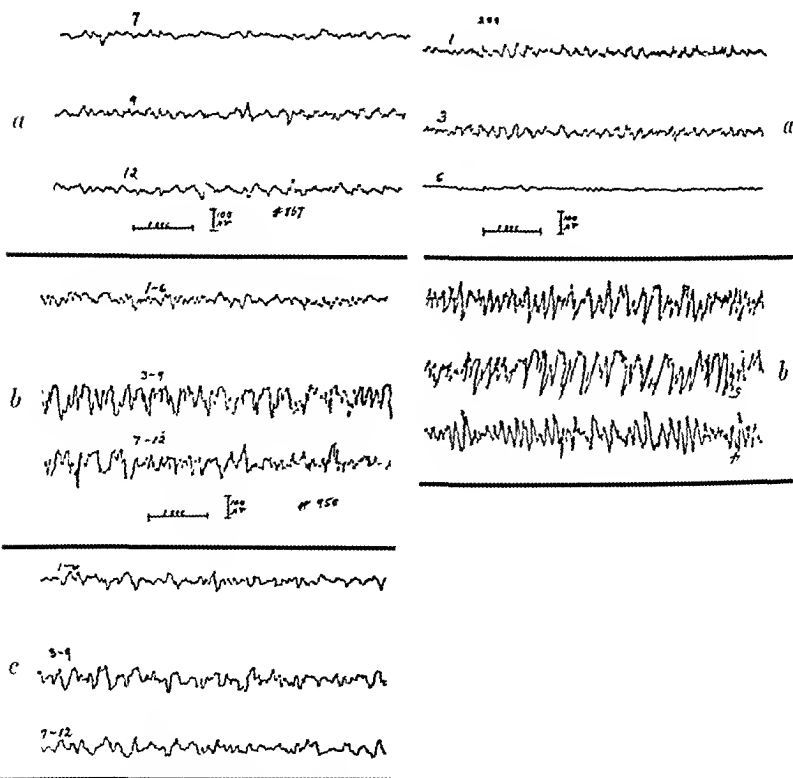


FIG. 7

FIG. 8

FIG. 7.—Patient (admitted to Longview Hospital, April, 1940; age 44) had had seizures since the age of 13 which were worse at her menstrual periods. She was psychotic, self-destructive and assaultive. *a*, May 26, 1940, control tracing, patient having seizures about 1 a month, psychotic symptoms and violent "spells." *b*, July 31, 1940, dilantin, 1 capsule t.i.d., for a month or more. She was having rare seizures, less than 1 in 2 months and was coöperative and helpful. She had a dilantin rash, but medication was resumed with continued benefit and no return of the rash. *c*, October 25, 1940, tracing made before patient was released. She was subsequently discharged from the hospital very much improved. She was able to do her housework and had had no seizures for over 6 months at the last report.

FIG. 8.—Patient (admitted to Longview Hospital, April, 1936; age 22) had had seizures since age 16. She had seizures once weekly or oftener at the time of admission. Patient improved remarkably after treatment started. *a*, July 13, 1939, tracing was taken on the day the patient was allowed to go home on trial visit. She had been receiving phenobarbital, 1½ grains, once or twice daily for a year. She had had no seizures for 2 months or longer and there was none of the "organic confusion" which had been present on admission. Only medium and low voltage slow activity evident. *b*, February 12, 1940, tracing was taken when the patient was returned from trial visit after having neglected treatment for several months. She had seizures oftener than once weekly and was in a dirty, disheveled, confused condition. Patient subsequently improved again and was able to return home. Tracing shows marked epileptic activity between seizures. Treatment apparently was essential to maintain more normal E.E.G. status.

The corollary which it may reasonably be hoped can be derived from these observations is that adequate, vigorous, and above all sustained treatment of convulsive disorder in its early stages,

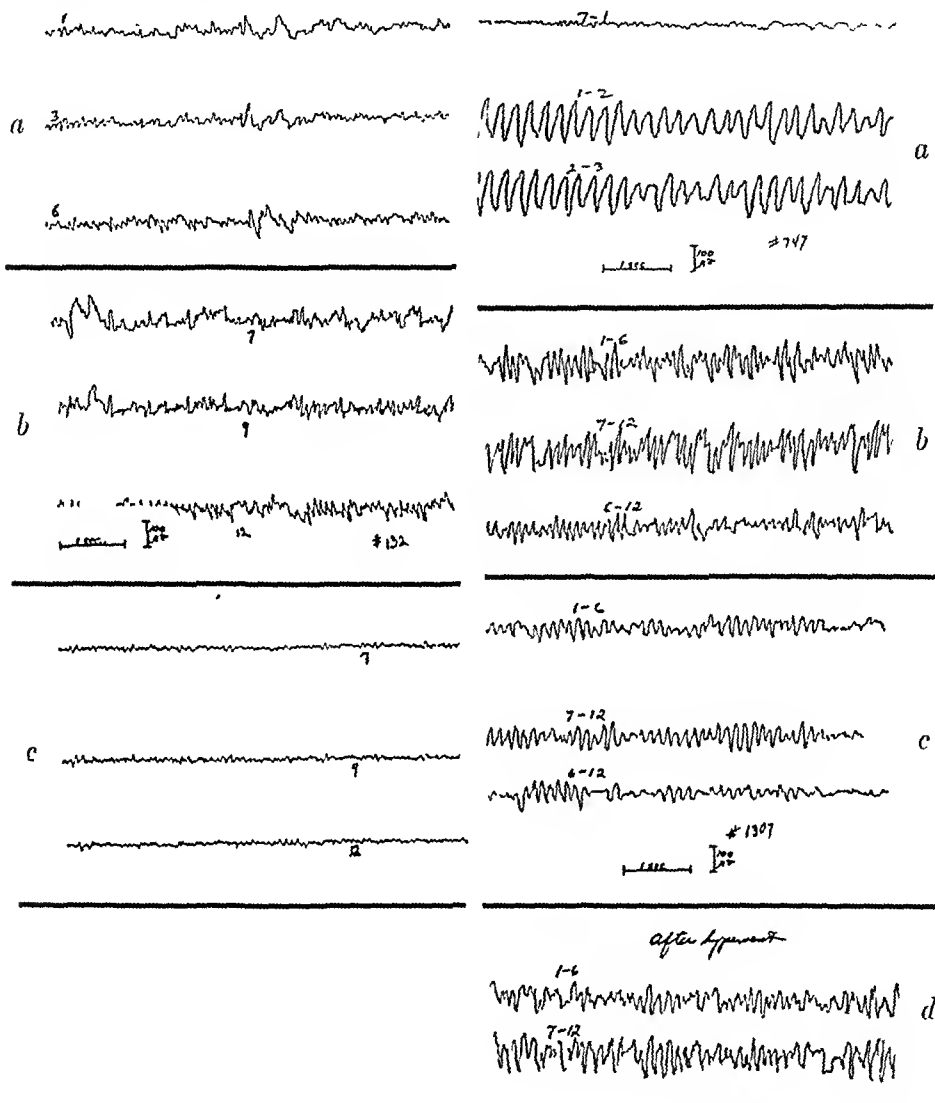


FIG. 9

FIG. 10

FIG. 9.—Patient (admitted to Longview Hospital, December, 1938; age 36) had spells of anger and quarreling and struck his mother. History of abnormal behavior since adolescence. He was said to have seizures in 1934 but inquiry at the hospital where he was at that time indicated that no seizures had occurred. *a* and *b*, April 5, 1939, control tracing. Only moderate, irregular pathologic activity evident. *c*, September 25, 1940, patient having dilantin, $1\frac{1}{2}$ grains b.i.d., for over 4 months. His behavior was very much improved. He had no further spells of anger or quarreling and was quite able to get along at home with his family. On several occasions he became disturbed when he discontinued medication but was perfectly normal at the time this tracing was made. Tracing appears normal and shows marked contrast with control record.

FIG. 10.—Private patient, age 12, who had had epileptic seizures for a year or more. *a* and *b*, March 20, 1940, seizures once weekly, none on the day of the tracing. Marked pathologic activity. *c* and *d*, July 24, 1941, dilantin, $1\frac{1}{2}$ grains twice daily, and phenobarbital, $\frac{1}{2}$ grain twice daily. She had had no seizures for several months and was making better than normal progress in her school work. Moderate pathologic activity evident only after hyperventilation.

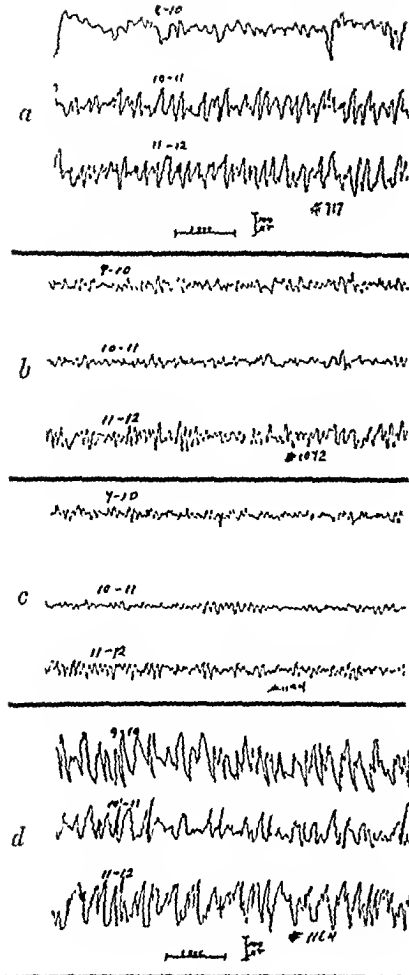


FIG. 11

FIG. 11.—A woman of 38 years with seizures and possible psychomotor equivalents, onset within a year. There was a question of an intracranial lesion because she had focal seizures from the right and sometimes from the left side and a suspicious pneumoencephalogram. The subsequent history after the last tracing recorded showed that no lesion was found on exploration of the brain, but the patient continues fairly satisfactory under treatment. *a*, March 6, 1940, no medication at this time. *b*, October 23, 1940, dilantin, 1½ grains t.i.d., and phenobarbital, 1½ grains once or twice daily, for several months. Marked relief was noted. Tracing within normal limits. *c* November 20, 1940, patient was asked to report after omitting medication for 1 week, but she stated that she was unable to do this because of the severity of psychomotor restlessness that occurred under such circumstances. She had, therefore, resumed taking dilantin and phenobarbital after only 2 days' omission of the treatment. The tracing, therefore, does not represent the untreated status. It appears normal. *d*, December 13, 1940. Patient remained off medication 2 days and reported when she stated that she "was feeling very bad" and could not hold out longer without treatment. It is apparent from the E.E.G. that her neurotic symptoms were psychomotor equivalents which the patient recognized as being abnormal.

FIG. 12.—Man, aged 42, admitted to Longview Hospital, April, 1940; first seizure occurred in 1920. The seizures consisted of psychomotor equivalents, amnesias and fugues. He denied having any major attacks but during observation on the ward he was seen to have localized and mild general seizures frequently. *a*, April 29, 1940, marked pathologic activity between seizures. *b*, May 17, 1940, dilantin, 3 grains twice daily for 2 weeks. *c*, June 18, 1940, dilantin, 3 grains for 6 weeks. *d*, July 22, 1940, dilantin, 3 grains twice daily, for 10 weeks. He had had no seizures since he was started on dilantin. He has been out of the hospital since February, 1941, and has made a good adjustment. He is supporting himself. He has had no further seizures. The last two E.E.G. are within normal limits.

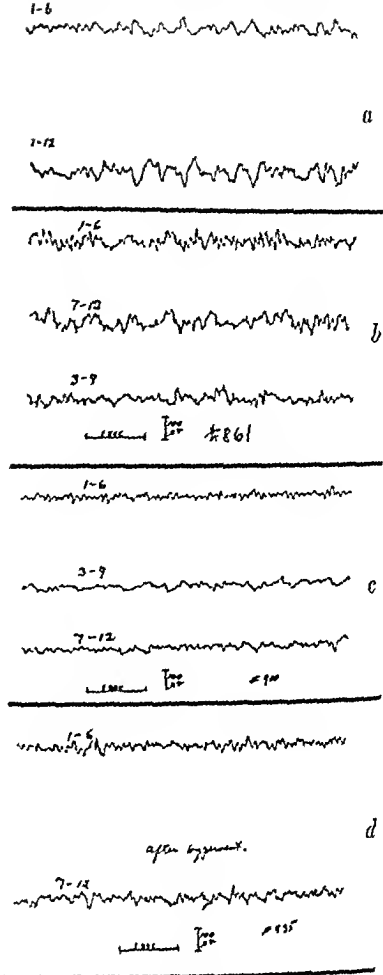


FIG. 12

preferably under E.E.G. control, may be able to restore patients to complete freedom from seizures and to protect them from late catastrophic sequelæ such as psychoses.

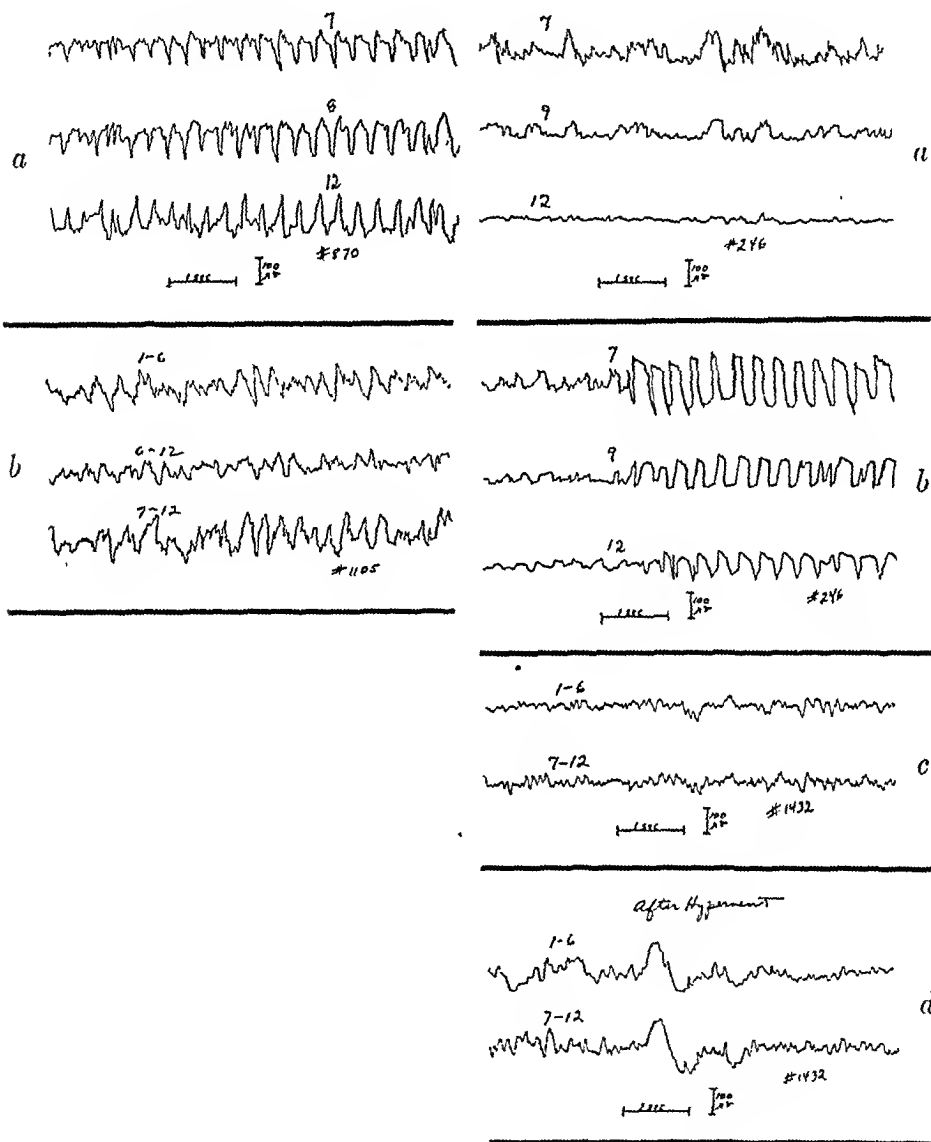


FIG. 13

FIG. 14

FIG. 13.—Boy, aged $2\frac{1}{2}$ years, private patient, who for several months had been having one or more “blank spells” daily. *a*, May 28, 1940, control tracing before tracing, showing *petit mal* attack. *b*, November 7, 1940, $\frac{1}{2}$ grain dilantin twice daily. No seizures had been observed for 4 months. Irregular high voltage 4/second activity not abnormal in a child of $2\frac{1}{2}$ years.

FIG. 14.—A girl aged 5, who had been having “blank spells” lasting up to $\frac{1}{2}$ minute several times for several months. *a* and *b*, portions of the tracing taken June 19, 1939, before treatment. Part of a typical *petit mal* attack is shown in *b*. *c* and *d*, February 27, 1942. Patient now aged 8, receiving dilantin, $2\frac{1}{2}$ grains daily in 3 doses, and phenobarbital, $\frac{1}{2}$ grain at bedtime for $2\frac{1}{2}$ years. She had had no seizures for a year or more, was making better than average progress in school. The tracing is normal for a child of 8.

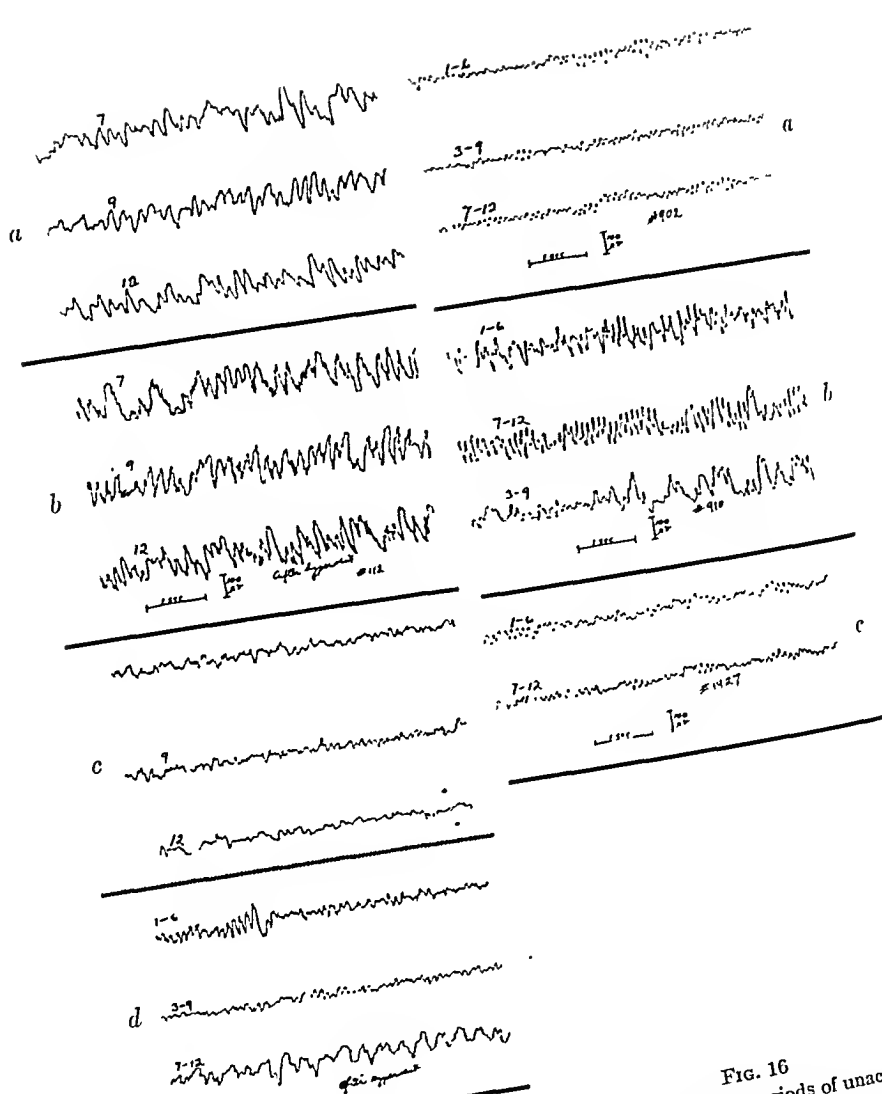


FIG. 15

FIG. 15.—Out-patient, age 18, who had had for some months periods of unaccountable behavior during which he scolded the doctors and nurses, jumped over the beds and subsequently had complete amnesia for the period of the attack. The clinical impression had been that he was suffering from a neurosis resulting from amputation of the left foot above the ankle. *a* and *b*, March 17, 1939, control tracing before treatment. Pathologic high voltage slow activity accentuated by hyperventilation. *c* and *d*, November 13, 1940, patient had been receiving dilantin, 1½ grains t.i.d., and had complete relief from attacks for over a year. Early in his treatment he stopped taking dilantin for a brief interval during which there was some recurrence of symptoms. This patient at no time had any clinical *grand mal* activity. E.E.G. shows normal activity at this time except after hyperventilation, and even here the voltage is not high.

FIG. 16.—A woman 25 years of age (admitted to Longview Hospital, June, 1940) reported seizures occurred about once a month. *a*, June 19, 1940, no seizures at this time. There is no record of treatment at this period. *b*, June 26, 1940, definitely not receiving treatment for at least 1 week. Marked epileptic activity in E.E.G. *c*, February 27, 1942, receiving dilantin, 1½ grains t.i.d., for 6 months. She had had no seizures in all this period. Before that when she stopped taking dilantin for 2 weeks she had had a seizure, so the drug was resumed and no further seizures occurred. Mental status was normal.

Conclusions. 1. Electroencephalographic (E.E.G.) and clinical observations on 16 cases of severe epilepsy are presented.

2. The course of every case was definitely modified by treatment, and in most cases markedly improved.

3. Clinical improvement was paralleled by E.E.G. findings.

4. Some cases of convulsive disorder can be completely relieved, and progressive deterioration prevented.

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MINERALS AND THE TOXEMIAS OF PREGNANCY

By CARL T. JAVERT, M.D.

ASSISTANT ATTENDING OBSTETRICIAN AND GYNECOLOGIST TO THE NEW YORK HOSPITAL;
INSTRUCTOR IN OBSTETRICS AND GYNECOLOGY, CORNELL UNIVERSITY
MEDICAL COLLEGE

CESIRA MACRI, B.S., M.A.

RESEARCH ASSISTANT

AND

KATHERINE KUDER, M.D.

ASSISTANT ATTENDING OBSTETRICIAN AND GYNECOLOGIST TO THE NEW YORK HOSPITAL,
INSTRUCTOR IN OBSTETRICS AND GYNECOLOGY, CORNELL UNIVERSITY
MEDICAL COLLEGE

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THE incidence of eclampsia and preëclampsia is much lower today than a decade or two ago, and prenatal care and adequacy in diet are usually credited with the reduced frequency. Nevertheless, one occasionally sees toxemia develop in patients receiving the very best antenatal care. Clinical observation of our antepartum patients indicates that mild and severe preëclampsia seldom occur in patients receiving iron therapy. It is the purpose of this communication to demonstrate our experience with 539 patients thus treated.

Present Study. The incidence of all types of toxemia of pregnancy in 27,405 pregnant women delivered in the Woman's Clinic of the New York Hospital, over a 10-year period (1932-1941), is 10.6%. The classification of the American Committee on Maternal Health has been employed. As indicated in Chart 1, there has been a decline in the total incidence during the past few years to about 7%. The reduction has been primarily in the mild and severe types of preëclampsia as shown in Charts 1 and 2. The renal, hypertensive and unclassified forms of toxemia have shown no significant variation. The incidence of eclampsia has not varied, but

JAVERT, MACRI, KUDER:

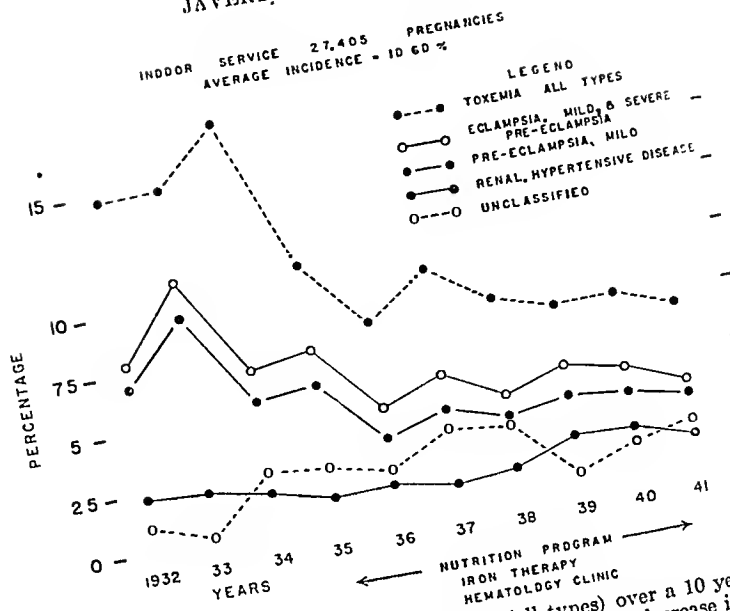


CHART 1.—Incidence of toxemia of pregnancy (all types) over a 10 year period, showing an appreciable decline. This appears to be due to a decrease in the incidence of mild and severe preeclampsia, since the incidences of the renal, hypertensive and unclassified types of toxemia showed no significant deviation.

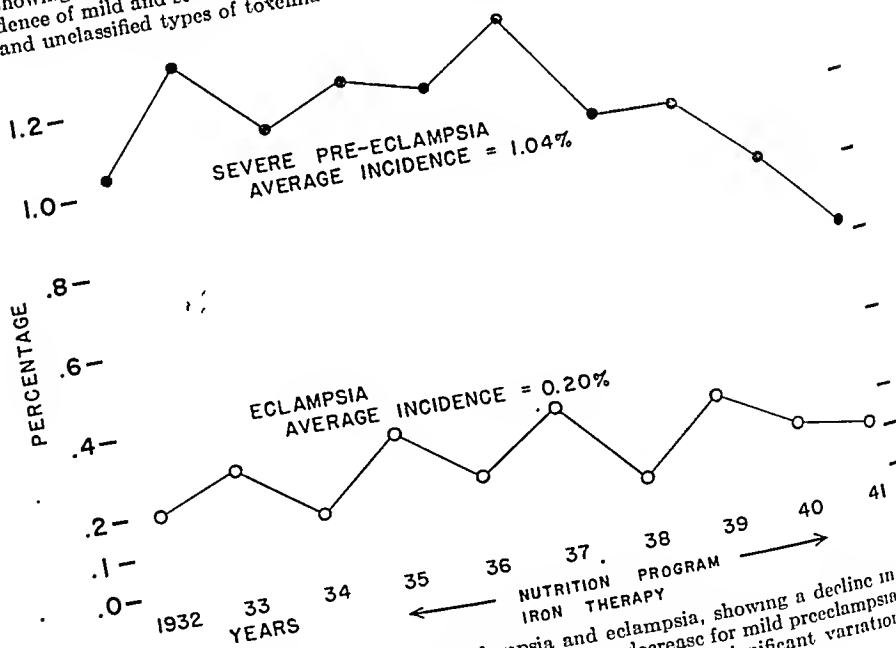


CHART 2.—Incidence of severe preeclampsia and eclampsia, showing a decline in the incidence of severe preeclampsia which follows the decrease for mild preeclampsia shown in Chart 1. The incidence for eclampsia shows little significant variation over a 10-year period.

it is 10 times less than the percentages reported in 1923 by Harrar⁶ from the Lying-In Hospital, and by Plass⁹ for the year 1927.

A nutritional program was instituted in 1935, the Nutrition Department of the New York Hospital collaborating in the regulation of the diet. At this time, a hematology clinic was also established and, as a result, various iron preparations were given to patients in both the antepartum clinic and the hematology clinic. There is ample evidence in the literature that mineral requirements are increased in pregnancy, hence the basis for the rather indiscriminate use of the iron therapy. Did these factors contribute to the lowered incidence of mild and severe preëclampsia?

The clinical study comprises 539 patients who received mineral supplement in the last trimester of pregnancy. Of these, 151 were given iron ammonium citrate, 212 ferrous sulphate, and 176 were placed on Endomin.* The daily intake of iron was 6 gm., 1.2 gm. and 72 mg. in these three groups, respectively. The hemoglobin response in many patients treated in the last trimester with either of the three preparations was sometimes *nil*. The reduced amount of hydrochloric acid in pregnancy may have been a factor in iron absorption. Moreover, Fowler⁵ and Barer² have observed that when 1 to 3 gm. are given daily, that from 26% to 32% of the iron is retained, presumably in the liver and spleen, with negligible change in the hemoglobin. Perhaps these factors prevent a rise in hemoglobin when requirements are increased, as in pregnancy.

The incidence of toxemia of pregnancy of all types in the patients receiving mineral supplement was 4.4%, or 24 cases in 539 patients. As shown in Table 1, this is less than half of the incidence reported for the control period. The chief reduction occurred in the total incidence of eclampsia and preëclampsia, namely, 1.68% *versus* 5.68%. When the treated patients developed toxemia, one was often able to discover that the medication had not been taken regularly, or was commenced just before the toxemia developed, so as to have had very little effect. As can be expected, the treatment produced no significant change in the incidence of renal, hypertensive and unclassified forms of toxemia.

TABLE 1.—INCIDENCE OF TOXEMIA OF PREGNANCY IN 539 PATIENTS HAVING DIET SUPPLEMENTED WITH IRON

Type of toxemia	Treated group		Clinic incidence 1932-1941 %
	No.	%	
Eclampsia	0	..	0 20
Preëclampsia, mild	8	1 5	4 64
Preëclampsia, severe	1	0 18	1 04
Renal and hypertensive disease	8	1 5	1 56
Unclassified	7	1 3	1 9
Acute yellow atrophy, vomiting, etc.	0	..	1 29
Total toxemia, all types	24	4 4	10 60

* Courtesy of Reed & Carnrick.

Crawford³ maintains that the hemoglobin parallels the hematocrit near term, at delivery, and early postpartum, and concludes that there is no shrinkage or swelling of the red corpuscles. This view is open to question, since microcytosis is often marked. The average cell volume and hemoglobin values of 200 patients are given in Chart 3. Determinations were made in the various weeks of gestation, at delivery and on the third day and six weeks postpartum day. The normal non-pregnant values of 44% for the cell volume and 95% for the hemoglobin were replaced by values of 34% and 80%, respectively, at term, indicating a greater percentage decrease in the cell volume than in the hemoglobin. Labor was associated with a slight increase in both which was maintained on the third post-

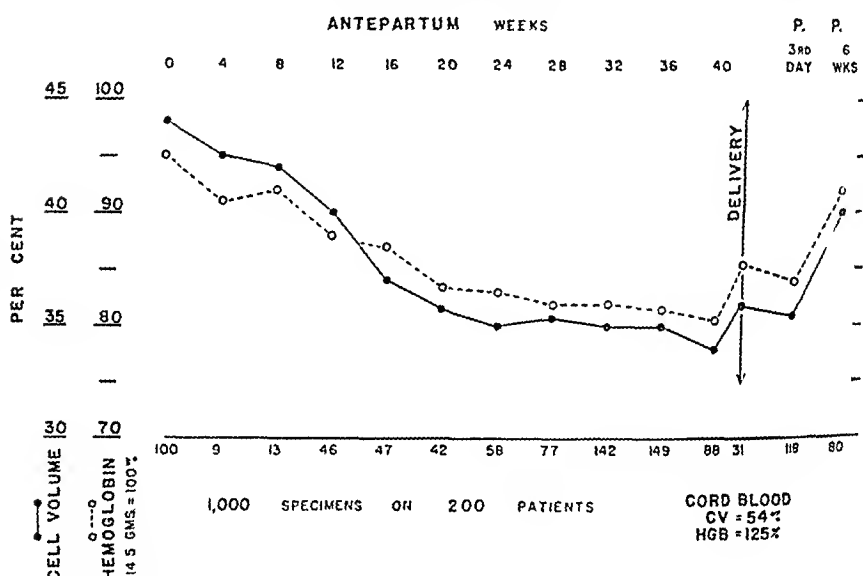


CHART 3.—Cell volume and hemoglobin values decrease in normal pregnancy.

partum day, in the absence of hemorrhage, infection and toxemia. At 6 weeks postpartum, the values were still a little below the non-pregnant values. This was not seen in the group of 8 patients receiving iron supplement during pregnancy whose values at term were: cell volume 41% and hemoglobin 93%, as shown in Chart 4. Ordinarily, such high values at term accompany toxemia with edema, as Diekmann,⁴ Crawford,³ Pastore⁵ and our own experience have shown. In toxemic patients with edema, the high cell volume before delivery is followed by a great drop postpartum, even though hemorrhage or infection have not occurred.

Diekmann⁴ states that anemia predisposes to edema, and that edema and hypertension occur more frequently in anemic patients. Pregnancy is associated with a physiologic anemia or "hydremia" resulting in a fall in the hemoglobin and cell volume as shown in

Chart 3. This change may also be due to increased fetal and maternal requirements, since the administration of minerals early in pregnancy prevented the marked decrease in 8 patients as shown in Chart 4. The lower cell volume at term may also be due to a decrease in red cell diameter, as microscopic examination of blood smears appears to indicate.

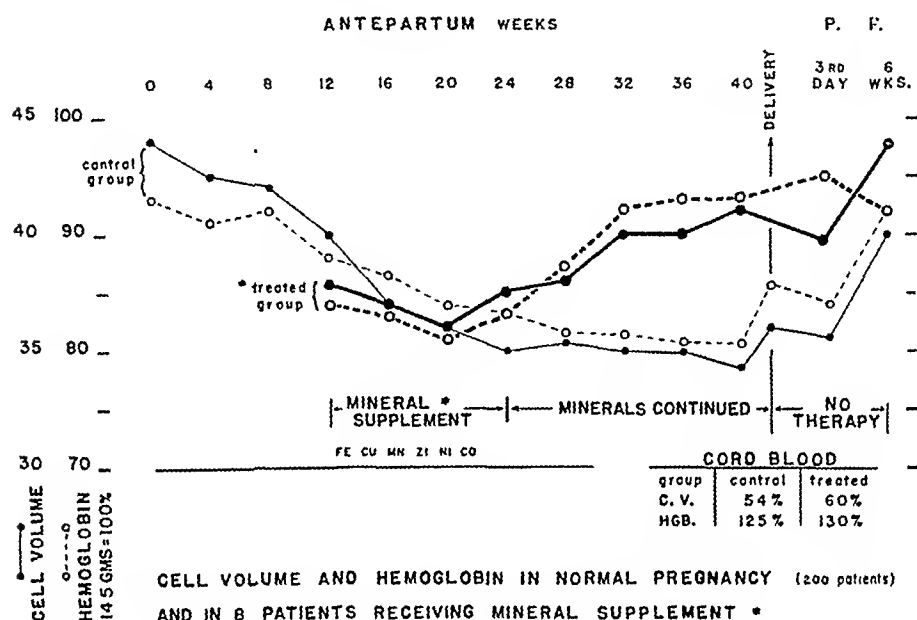


CHART 4.—Cell volume and hemoglobin values. Mineral supplement appears to prevent a decrease if started early in pregnancy.

TABLE 2.—MATERNAL AND FETAL DATA IN 176 PATIENTS RECEIVING A MINERAL SUPPLEMENT

	Treated patients	Clinic control
Maternal blood values at term:		
Cell volume	38 0%	34
Hemoglobin	84 0%	81
Body weight	69 4 kg.	72 2
Duration of pregnancy	39 9 wks.	40
Primiparas	48 0%	52
Multiparas	52 0%	48
Toxemia, all types	4 8%	10 7
Blood loss	183 cc.	244
Fetal—cord blood values:		
Cell volume	59 0%	54
Hemoglobin	122 0%	126
Weight:		
At birth	3388 gm.	3220
Third day	3205 gm.	3020
Tenth day	3407 gm.	3220
Stillbirths	1 4%	3 5
Excessive sized infants	10 0%	11
Premature infants	3 0%	2

Mineral Supplement Study. A mineral supplement* was given to 176 patients on an adequate diet during the last trimester of pregnancy, and data on this series of patients is provided in Table 2.

* Endomin, courtesy of Reed & Carnrick.

The daily dosage of 3 tablets, t.i.d., provided 72 mg. iron, 5.4 mg. copper, 2.7 mg. zinc, 3.6 mg. manganese, 0.27 mg. nickel and 0.27 mg. cobalt. The treated patients had a higher cell volume at term, indicating a hematinic action. The increase in hemoglobin was not appreciable, probably because of the increase in the number of red cells that were filled, and perhaps iron storage took place. Had treatment been started earlier in pregnancy, higher values might have been obtained, as indicated by the study of 8 patients shown in Chart 4. The weight gain was nearly 3 kg. less (6 pounds) in the treated patients than in the control group. This may be indicative of less accumulation of tissue fluid and, therefore, the contributing factor in the lower incidence of toxemia, namely, 4.8%. The distribution of primiparas and multiparas was essentially the same in both groups of patients. The control values or percentages are those ordinarily employed in the Woman's Clinic, and most of them are available in Stander's¹³ textbook. The average blood loss in the third stage of labor and the incidence of postpartum hemorrhage were not increased in the treated patients.

The infants born to the treated mothers had a definite increase in the cell volume of the cord blood, but not an appreciable increase in the hemoglobin. Perhaps the same factors were responsible as have been described above for the mothers. The average weight at birth was slightly greater than in the control group, as were the weights on the third and tenth days of life. The number of excessive sized and premature infants was not increased. There were fewer stillbirths in the treated group.

Discussion. The physiochemical causes of cellular swelling in pre-eclampsia are beyond the scope of this paper. Clinically, five factors may be borne in mind: (1) swelling of the kidney parenchyma is limited by a tough renal capsule; (2) the cerebral swelling is limited by the bony skull; (3) clinical improvement when the infant dies *in utero*; (4) maternal liver damage; (5) a seasonal variation of the disease (highest in the winter).

The clinical effect of an adequate diet and the administration of iron and other hematinic minerals in lowering the incidence of pre-eclampsia has been referred to above. There is experimental evidence showing a possible relationship of iron to pre-eclampsia. Stander, Duncanson and Sisson^{13,14} found 51 mg. of iron per 100 cc. of whole blood in non-pregnant subjects. In normal pregnancy, Sachs¹⁰ and his coworkers report a value of 41 mg. In pre-eclampsia, Stander^{13,14} *et al.* obtained a value of only 34 mg. Clinical evidence of iron deficiency before delivery is not confirmed by the unusually high cell volume and hemoglobin values in patients with pre-eclampsia. However, it becomes more evident postpartum when a marked drop in both cell volume and hemoglobin takes place.

What mineral deficiencies affect the nutrition and structure of organs, especially the liver? In rats, Alt¹ found a markedly lowered

iron content of the liver in pregnancy. According to Schultze and Kuiken,^{11,12} deficiency in both iron and copper decreased the catalase activity of the liver, kidney and blood of the rat. Wachtel¹⁵ and his coworkers found that rats on a zinc deficient diet had an elevation in the blood uric acid from 3.9 to 6.1 mg. Are deficiencies in these minerals contributory to the liver damage and associated changes which characterize preëclampsia? Clinically, the use of good diet and a mineral supplement appears to lower the incidence of the disease, as shown in Chart 2, which places adequate nutrition in the foreground as a preventative measure.

In years gone by, chlorosis was a common condition in adolescent girls, and today "green sickness" has virtually disappeared. Improved diet, sunlight, fresh air, and correction of iron deficiency have been credited with this result. The occurrence of chlorosis in young girls, often precipitated by the increased requirements produced by the onset of menstruation, may be analogous to the increased requirement in pregnancy, since preëclampsia is more common in primiparas and elderly primiparas. The decreased incidence of preëclampsia following a nutritional program of adequacy points to a deficiency in the retention of iron, and other hematinic minerals, as a possible underlying factor in this condition. The work of Barer² and Fowler⁵ is significant in this regard. They concluded from iron balance studies that the loss of 5.28 mg. of iron per period was not met by the ordinary diet, and that such continued loss may deplete the iron reserves and ultimately result in anemia. If under such circumstances patients became pregnant, the increased fetal and maternal requirements are likely to precipitate a physiologic anemia. Such patients are more apt to develop edema and hypertension, and so perhaps preëclampsia. Administration of iron to avoid depletion of the storage appears to prevent this type of toxemia from developing, as stated above and also observed by Moore and Pillman-Williams.⁷

Conclusions. 1. Establishment of a nutritional program in the antenatal clinic has been accompanied by a decrease in the number of patients having mild and severe preëclampsia.

2. Physiologic anemia of pregnancy may be evidence of decreased absorption, increased requirements, microcytosis and depleted reserves of iron and other hematinic minerals and, therefore, may not be entirely due to hydremia.

3. There appears to be an association of physiologic anemia, edema, hypertension, and possibly preëclampsia.

4. The incidence of mild and severe preëclampsia in 576 patients receiving a dietary supplement of iron was 1.68%, whereas, over a 10-year period, 5.65% of the patients had these two types of toxemia.

5. The incidence of renal, hypertensive and unclassified forms of toxemia was not changed in the treated patients, nor have they varied appreciably since the nutrition program was inaugurated.

6. A mineral supplement containing iron copper, zinc, manganese, nickel and cobalt is indicated when deficiency is proven or suspected.

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THE TREATMENT OF LEAD POISONING BY SODIUM CITRATE

By SEYMOUR S. KETY, M.D.*

AND

T. V. LETONOFF, M.S.

PHILADELPHIA, PA.

(From the Division of Biochemistry and the Medical, Neurological and Surgical Services of the Philadelphia General Hospital)

LEAD poisoning, despite our knowledge of its etiology and pathogenesis, remains one of the most important of occupational diseases. A new and effective agent for the treatment of this condition is described in the present study, which represents the results of the therapy of lead intoxication by means of sodium citrate in 15 cases of lead poisoning in adults.

Although Aub and his group¹ used sodium citrate in an experiment on lead excretion in 1925, it was employed merely as a source of alkali and not for any specific effects due to the citrate ion. In 1940 Kety² showed that in dilute solution sodium citrate exerts a powerful solvent effect on the extremely insoluble tertiary lead phosphate. Subsequent investigation demonstrated that citrate forms with lead a soluble complex of extremely low dissociation. By determining the value of the constant of this dissociation it was shown that the citrate ion normally present in human blood might have an important function in the transportation and excretion of

* Now at Massachusetts General Hospital, Boston, Mass.

lead. The suggestion was offered that the administration of citrates might constitute a safe and effective therapy in plumbism.³ In a preliminary clinical investigation of the treatment of lead poisoning with sodium citrate previously reported,⁴ the authors found a marked reduction in blood lead concentration and a rapid clinical improvement following citrate therapy.

Material. Included in the present report are all adult patients under our observation admitted to the wards of the Philadelphia General Hospital from August 1940 to May 1942, in whom a primary diagnosis of lead poisoning was established. In every case there was a known industrial exposure to lead, an abnormally high concentration of lead in the blood before treatment and sufficient cardinal manifestations of the disease (colic, anorexia, weight loss, constipation, neuropathy, anemia, basophilic stippling and lead line) to permit an unequivocal diagnosis. The occupations represented are of interest: 7 patients were employed in lead smelting plants, 3 were battery workers, 1 was a painter, 1 a paint mixer, 1 a plumber, 1 an oxyacetylene torch operator who had been cutting through heavily painted steel plates, and 1 an attendant in a shooting gallery so heavily contaminated with lead that the floor dust was collected and sold for salvage of this metal.

Method. Nine of the 15 patients for an interval after admission received no medication likely to influence lead metabolism. Pain was controlled by tincture of belladonna, codeine or morphine, constipation treated with cascara sagrada, and no other drugs were administered. In this manner control periods were obtained and used as a means of better evaluating the citrate treatment. During the period of citrate therapy the patients were given 4 or 5 gm. of sodium citrate dissolved in 1 ounce of water, 3 or 4 times daily. Four patients presenting severe colic on admission were given at once 50 cc. of a sterile 2.5% aqueous solution of sodium citrate by vein. No other drugs, with the single exception of cascara, were administered or even found necessary during the citrate treatment. All patients received the regular hospital diet throughout the study.

On admission and at intervals thereafter blood lead concentrations were determined by the method of Letonoff and Reinhold⁵ slightly modified.⁶ By this method normal blood yields 0 to 0.05 mg. of lead per 100 gm. of whole blood. Hemoglobin values (reported as gm. per 100 cc.) were determined photocolormetrically by the method of Sanford, Sheard and Osterberg.⁷

Results. Blood Lead Concentration. Changes in blood lead concentration before and during citrate therapy are presented in Figure 1. It is seen that whereas there is no consistent change in blood lead before citrate, the administration of this substance is accompanied by a marked fall in blood lead concentration in every case, so that after 20 days of citrate therapy there is no value over 0.1 mg. per 100 gm. Table 1 represents a summary of the statistical analysis of these data. No significant change in blood lead was found before treatment, while after 5, 10, 15 and 20 days of citrate therapy there was a highly significant reduction in blood lead concentration. In a few patients (Cases 3, 5, 9, 11 and 12) the initial fall in blood lead under citrate is followed by a secondary rise during the course of the therapy. This rise, however, is never great, the

patients were symptom-free during its occurrence, and where it was possible to continue the observations (Cases 3, 5, 9 and 12) the blood lead concentrations fell once more.

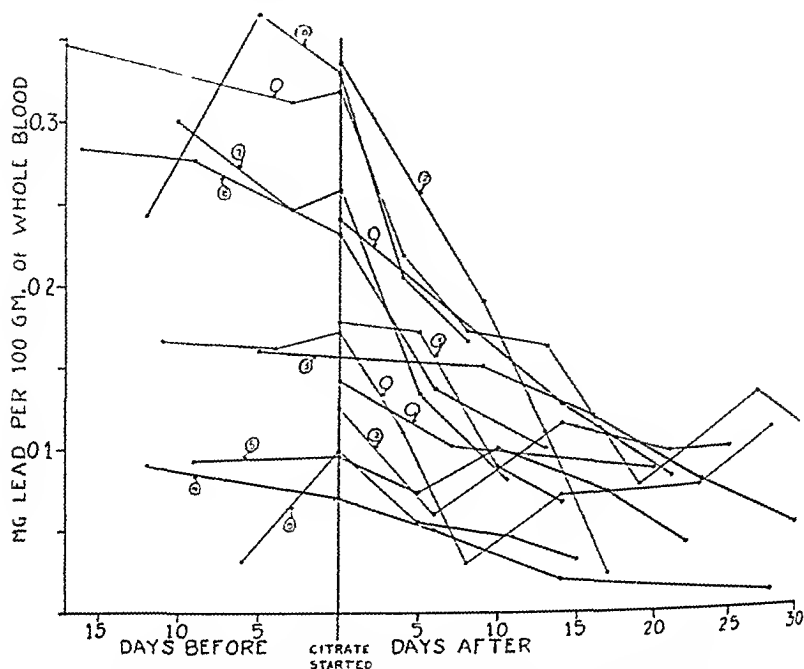


FIG 1 —Changes in blood lead concentration before and after treatment by sodium citrate. The vertical line indicates the beginning of citrate therapy.

TABLE 1 —AVERAGE CHANGE IN BLOOD LEAD CONCENTRATION BEFORE AND DURING CITRATE THERAPY AND ITS STATISTICAL TREATMENT

Duration	No. cases	Average change blood lead γ Pb/100 gm	Standard error	t*	p*	Interpretation
<i>Without Treatment</i>						
5 days	8	+ 9.4	± 14.4	0.65	0.5	No change
10 days	6	- 0.17	± 21.1	0.008	0.99	No change
<i>Under Citrate Treatment</i>						
5 days	14	-58.9	± 11.7	5.03	<0.01	Highly significant fall
10 days	13	-82.7	± 16.4	5.04	<0.01	Highly significant fall
15 days	10	-89.3	± 25.9	3.45	<0.01	Highly significant fall
20 days	8	-89.3	± 24.8	3.60	<0.01	Highly significant fall

* "t" is a value obtained by dividing a mean by its standard error, and was introduced by R. A. Fisher in his so-called table of "t" as an index of statistical significance for small samples. "p" is a value obtained from Fisher's table for each value of "t" and represents the likelihood that the result in question could have arisen simply by chance. Values of "p" below 0.05 are usually regarded as statistically significant while values of the order of 0.01 or less are considered highly significant.

Three patients (Cases 1, 3 and 9) were seen again several months after the conclusion of citrate treatment. In each the blood lead concentration at that time was practically within normal limits (0.06, 0.05, 0.053 mg. per 100 gm. respectively).

Lead Colic. Twelve of the 15 patients had colic of some degree among their presenting symptoms. In the period before citrate

therapy this was controlled by belladonna or opiates. After the institution of citrate treatment, these drugs were not necessary and in no case was there a recurrence of abdominal pain. Four patients (Cases 8, 12, 13 and 15) were admitted with severe colic of several days duration and in these sodium citrate was given intravenously. Fifty cc. of a sterile 2.5% aqueous solution was administered very slowly since this route is not without danger. No untoward reaction was encountered, and in 2 of the patients (Cases 8 and 15) there was a dramatic disappearance of all abdominal pain after a few minutes. Citrate was continued by mouth and within 24 hours all patients experienced complete relief which persisted throughout the period of observation.

Anorexia. Eleven patients gave a history of anorexia, associated in some with weight loss. During citrate therapy there was a marked increase in appetite in all 11 cases, and 3 patients who kept records of their weights noticed a steady gain during and after citrate therapy.

Neuropathy. Only 2 patients exhibited true peripheral neuropathy. One (Case 4) had unilateral foot drop which improved slightly before citrate therapy and disappeared entirely after 2 weeks of sodium citrate alone. The other (Case 2) presented an extremely severe and extensive paralysis involving all extremities and causing total incapacitation. He received sodium citrate, but also brewer's yeast and physiotherapy. After 4 weeks he was able to walk and to use his hands, although he was still unable to raise his arms.

Constipation. Seven patients gave constipation as a major complaint. This was the one symptom which did not respond to citrate therapy. During citrate treatment 1 patient (Case 15) showed marked improvement with regular bowel movements without laxatives, 3 patients showed slight improvement, and 3 noted no improvement.

Basophilic Stippling. A marked decrease in the number of stippled cells was found at the end of treatment in every one of 6 cases examined for these cells before and after citrate therapy.

Anemia. All patients in the series had evidence of moderately severe anemia. In 10, hemoglobin was determined before and after treatment. Of these, 3 showed a marked increase, 3 a slight increase, and 4 a slight decrease after citrate therapy. No patient received medication containing iron during the study.

General Condition. All patients experienced, and most spontaneously reported, a definite general improvement and feeling of well-being in addition to improvement in specific symptoms, soon after the institution of citrate therapy.

Reactions and Other Effects. No reactions attributable to sodium citrate or to lead were observed during our entire experience with this treatment in which some patients received 20 gm. of sodium citrate daily for several weeks. Contrary to expectation, no symp-

toms of alkalosis appeared and there was no significant change in alkali reserve or total base of the blood (Table 2). No patient experienced a recurrence or aggravation of the symptoms of lead poisoning while receiving citrate therapy, whereas the occasional appearance of such reactions is alleged to be a danger in the usual deleading methods.

TABLE 2.—CHANGES IN CERTAIN BLOOD SERUM CONSTITUENTS BEFORE AND DURING CITRATE ADMINISTRATION

Experiment	Duration of citrate treatment (days)	CO ₂ (vol. %)	Cl (mg. %) (NaCl)	Protein (%)	Ca (mg. %)	Inorg. P (mg. %)
1	Before	57	565	6.6	10.8	4.4
	7	53	598	7.0	10.8	4.4
	14	63	610	6.2	9.8	4.2
2	Before	57	610	6.8	10.1	6.0
	5	58	585	7.1	10.1	4.2
	12	53	600	7.3	10.5	4.2
	15	58	585			
3	Before	50	550	7.3	9.9	3.8
	Before	54	600	6.6	9.6	3.4
	9	52	592			
4	Before	52	585	7.2	10.0	4.0
	Before	58	600	6.7	9.6	4.0
	7	56	585	6.6	9.4	3.8
	10	59	592			
5	Before	9.8	3.4
	Before	10.6	4.2
	5	10.7	4.2
	11	11.4	3.8
6	Before	10.3	3.4
	5	10.9	4.0
	10	10.0	3.6

In an attempt to determine whether the effects of citrate on lead poisoning were mediated through changes in the acid-base balance or calcium or phosphorus metabolism, some studies were made of changes in certain blood constituents before and during continued ingestion of sodium citrate. No consistent changes were observed (Table 2).

Case Reports. CASE 1. F. S., white male, 49, an oxyacetylene torch operator, had 3 previous admissions to this hospital in 1939 and 1940 for lead colic which was resistant even to intravenous calcium. Fourth admission, 8-24-40, with mild intermittent colic, constipation, anorexia, muscle cramps, lead line. Discharged 9-9-40 asymptomatic after 14 days of citrate therapy. Followed as out-patient from 10-26 to 11-16-40, during which time he received citrate and remained free of symptoms except for constipation. Last seen 2-2-41 when he was admitted for another condition, at which time his blood lead was 0.06 mg. per 100 gm.

CASE 2.—W. M., white male, 60, a painter for 30 years, admitted 11-4-40 with complete quadriplegia of 3 weeks' progression, weight loss, vomiting. Discharged 12-5-40 after 27 days of citrate therapy, along with brewer's yeast and physiotherapy. Clinical condition on discharge much improved, able to walk and to use hands, weakness of shoulder girdle persisted. Stippled cells dropped from 4+ to 1+ under treatment.

CASE 3.—G. K., negro, 28, smelter for 5 years, admitted 12-25-40 with severe colic, vomiting, muscle cramps. Exploratory laparotomy done on admission with negative findings but followed by subsidence of colic. Citrate therapy started 1-11-41. After 4 days patient felt considerable

improvement. Followed as out-patient from 1-27 to 4-28-41 during which time he received sodium citrate only, gained 11 pounds and noted marked general improvement. Hemoglobin rose from 8.5 to 11.8 under citrate therapy. Last seen 3-24-42 when blood lead was 0.05 mg. per 100 gm.

CASE 4.—C. C., white male, 53, storage battery worker for 10 years, admitted 3-12-41 with paresthesias of the extremities, muscle cramps, unilateral foot drop, constipation. On regular diet and no medication he improved slightly, but foot drop and constipation persisted. On 3-25-41 sodium citrate therapy was begun. After 2 weeks there was marked general improvement, the foot drop disappeared and the constipation was considerably improved. During treatment his hemoglobin dropped from 13.5 to 12 gm. He was discharged 4-26-41 with no signs of lead intoxication.

CASE 5. J. N., negro, 32, smelter for 9 years, admitted 6-5-41 with moderately severe colic, paresthesias, generalized weakness, anorexia, vomiting, lead line. He was alleged to have received small doses of potassium citrate for a few days before admission without improvement. Immediately on admission he was given calcium gluconate intravenously and sodium citrate by mouth and was fairly comfortable for 24 hours. All specific therapy was then stopped and his pains were controlled by opiates and belladonna. After 3 days there was considerable improvement. On 6-16-42 sodium citrate therapy was resumed. He continued to improve and was discharged 7-8-41. Hemoglobin was 8.8 gm. on admission and 8.5 gm. on discharge.

CASE 6. A. R., negro, 36, storage battery worker for 6 years, admitted 6-5-41 with moderately severe colic, severe anorexia, lead line. For 6 days he was given no specific medication, his symptoms persisted and required belladonna daily and opiates occasionally. On 6-11-41 citrate therapy was begun. In 3 days he was symptom-free and he remained so until his discharge on 6-27-41. During citrate therapy his hemoglobin rose from 10.8 to 14 gm.

CASE 7. J. W., negro, 28, smelter for 9 years, admitted 6-27-41 with intermittent colic, anorexia, metallic taste, vomiting, constipation, paresthesias, muscle cramps. He was given no specific medication for 13 days during which he required occasional opiates. On 7-10-41 citrate therapy was started. The metallic taste disappeared, all pains and cramps ceased, his appetite improved but he still required mild laxatives. He stated he had not felt as well for 5 years at the time of his discharge, 7-21-41. During citrate therapy his hemoglobin rose from 9.4 to 10.9 gm.

CASE 8. J. K., negro, 33, paint mixer for 2 years, admitted 11-24-41 with severe colic, radial weakness, constipation, anorexia, lead line. He was given immediately by vein 50 cc. of 2.5% sodium citrate with dramatic cessation of pain even before the injection was completed. Five hours later the colic recurred and the intravenous injection was repeated with the same result. Following this injection he received 5 gm. of the salt by mouth and remained comfortable for the next 18 hours. He was given no other specific medication for 15 days, during which he required belladonna and occasionally opiates for mild recurrences of colic. On 12-11-41 sodium citrate therapy was resumed by mouth. There were no recurrences of colic, anorexia and muscular weakness disappeared and his constipation was slightly relieved. He was discharged 12-23-41.

CASE 9. B. C., white male, 34, storage battery worker 20 years, admitted 2-19-42 with anorexia, weight loss of 40 pounds in previous year, inconstant colic, constipation, lead line, metallic taste. Stippled cells on admission 3+. During control period from 2-19 to 2-28-42 patient did not notice any appreciable change in his symptoms. On 2-28-42 citrate therapy was started. Within 3 days there was great subjective improvement; anorexia, abdominal pains, metallic taste had all disappeared. Discharged 3-8-42

with an occasional stippled cell in the blood smear. Followed as an out-patient on continued citrate therapy with no recurrence of symptoms, continued weight gain, excellent appetite. Hemoglobin rose from 9 to 10.1 gm. under therapy. Last seen 5-15-42 when he was symptom-free.

CASE 10. W. B., negro, 34, smelter 2 years, admitted 3-14-42 with intermittent colic, general weakness, anorexia, weight loss, vomiting, lead line and 4+ stippling. During control period he received belladonna, had no abdominal pain and noticed slight general improvement. On 3-28-42 citrate therapy was started. The patient was discharged 4-5-42 with great improvement in appetite and strength and an occasional stippled cell in the blood smear. Hemoglobin rose from 7 to 8.2 gm. during citrate therapy.

CASE 11. H. C., white male, 52, plumber for 30 years, admitted 3-16-42 with anorexia, constipation, intermittent colic, weight loss, general weakness, lead line and 4+ stippling. During control period on belladonna, his abdominal pains ceased but there was not much general improvement. On 3-28-42 sodium citrate therapy was started. By 4-2-42 there was marked improvement in appetite and the feeling of lassitude had disappeared, but constipation persisted. Until the time of his discharge 4-28-42 there was no recurrence of any symptoms of lead poisoning except persistent constipation, and at that time his stippled cells were 1+. Hemoglobin rose from 8.2 to 11.7 gm. during citrate therapy.

CASE 12. R. G., white male, 30, shooting gallery attendant for 6 months, admitted 4-7-42 with anorexia, constipation, vomiting, lead line, stippling 4+, and very severe colic of 5 days' duration. He was immediately given 50 cc. of 2.5% sodium citrate by vein with a slight increase then a slight decrease in the severity of the colic. Citrate therapy was continued by mouth. Within a few hours there was a temporarily longer intervals. After 24 hours the pain completely and permanently disappeared. On discharge 4-15-42 his appetite had greatly improved and his constipation was gone. Stippled cells were 1+. Hemoglobin dropped from 11.3 to 10.5 gm. during therapy. He was followed as an out-patient on continued citrate therapy and was last seen 5-2-42, feeling well, although his blood lead was 0.1 mg. per 100 gm.

CASE 13. J. P., negro, 31, smelter 3 years, admitted 4-29-42 with severe colic, anorexia, weakness of grip, lead line. On admission he was given morphine and atropine with no relief and then 50 cc. of 2.5% sodium citrate intravenously. There was no change in the severity of the colic and citrate was continued by mouth for 12 hours, at the end of which time he was perfectly comfortable. From 4-30 to 5-9-42 he received no medication and experienced occasional recurrences of colic. On 5-9 citrate therapy was resumed and he was discharged 5-11-42 with no symptoms of lead poisoning. He was still asymptomatic when last seen on 5-22-42.

CASE 14. D. H., white male, 21, smelter for 1 year, admitted 5-8-42 with moderately severe colic, anorexia, vomiting, constipation, lead line. He was given sodium citrate by mouth and within 12 hours the colic had disappeared. He was discharged free of symptoms on 5-11-42 but did not return for further study.

CASE 15. F. J., negro, 42, smelter for 14 years, admitted 5-13-42 with moderately severe colic, anorexia, weight loss, constipation, metallic taste, lead line and 4+ stippling. He was immediately given 50 cc. of 2.5% sodium citrate by vein with dramatic cessation of colic a few minutes after the administration. Citrate was continued by mouth and within 5 days there was a remarkable return of appetite, a weight gain of 5 pounds, daily bowel movements and disappearance of metallic taste, although the blood lead was still high. This patient had a urea clearance of 22 which

may have accounted for the slow fall in blood lead in the first few days. He was discharged 5-20-42 completely symptom-free, having gained 11 pounds with stippled cells of 1+ in the blood smear. Hemoglobin on admission 9 and on discharge 8.2 gm. Last seen 5-27-42 when he was still free of all symptoms.

Discussion. Although the removal of patients from exposure to abnormal quantities of lead during these studies is a factor to be considered in explaining the results, it can hardly be of great importance. This is demonstrated by the lack of significant change in blood lead or symptoms during the control periods.

The results obtained in this clinical study appear to be compatible with the evidence concerning the pharmacologic action of citrates derived from physico-chemical considerations. From a knowledge of the nature of the lead citrate complex and its degree of dissociation, it was calculated³ that a considerable fraction of the diffusible lead in the blood stream must exist as the lead citrate complex even without citrate therapy, since the citrate ion occurs in significant amounts in normal blood.⁹ Being diffusible, this fraction should be available for excretion through the kidney. Since citrate is known to be metabolized by the liver,^{10,11} it is possible that after the lead citrate complex has been transported to the liver and the citrate utilized, the lead residuum may be discharged in the bile. Thus the citrate normally present in the blood may serve as a mechanism of some importance in the excretion of lead. When large doses of sodium citrate are taken by mouth, the blood citrate content is known to increase. By physico-chemical necessities this should result in an increase in the diffusible blood lead fraction at the expense of the non-diffusible lead of the blood and eventually of the tissues. It can be shown, furthermore, that during this process the lead ion concentration of the blood cannot increase.³ Thus the administration of sodium citrate to patients with lead poisoning should result in a rapid clearing of the blood lead content. Ultimately, an extraction of deposited lead from the tissues should occur, accompanied by an amelioration of symptoms and an increased excretion of lead in the urine and feces.

Smith,¹² commenting upon sodium citrate therapy, arbitrarily groups it among those substances which cause lead storage. It is difficult to evaluate this conclusion, since it is based upon a single case given both calcium and sodium citrate without any measurements of lead excretion. The authors, in studies of lead excretion in 9 cases of plumbism before and during citrate administration,¹² find a significant increase in urinary and fecal lead excretion during citrate administration.

Summary. 1. The results of citrate therapy on 15 cases of lead poisoning in adults are presented.

2. There is a marked and significant fall in blood lead concentration during citrate administration.

3. There is an immediate and persistent amelioration of symptoms of lead poisoning during and after citrate therapy.

4. Intravenous administration of sodium citrate relieved severe colic immediately in 2 of 4 patients presenting this symptom.

5. No reactions or ill-effects of sodium citrate, or recrudescence of symptoms of lead poisoning were observed at any time.

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THE SPECIFIC DYNAMIC ACTION OF PROTEIN

BY MARTIN S. ABEL, M.D.

PHILADELPHIA, PA.

It is well known that following the ingestion of protein, and to a lesser extent fat and carbohydrate, there is for some time a marked increase in bodily energy output. This phenomenon, the specific dynamic action (SDA) of protein, has been the subject of considerable experimentation, which has been largely inconclusive in discovering any relation between the SDA and the endocrine systems.

The influence of the thyroid, because of its specific influence on basal metabolism, has been especially studied with regard to SDA, and the results have been controversial. In 1895 Magnus-Levy¹ and in 1916 DuBois² found the SDA of protein and carbohydrate practically within normal limits in hyper- and hypothyroids. Other experiments, also using large protein test meals, showed a slight increase in the SDA of protein in thyroid disease. However, all these early investigations were based on small numbers of cases.

and the measure of the SDA was usually a single metabolic reading despite the fact that after a large protein meal the increase in metabolism lasts for many hours.

Goldzieher and Gordon⁷ used a small protein meal, consisting of the whites of 2 eggs, toast and tea, with presumably a more limited increase in metabolism which they felt could be adequately measured by the difference of 2 basal metabolic rates (BMR's) before and 2 hours after the test meal. With this technique in a large series of cases only a very slight increase was found in SDA in thyroid hyperfunction. Guns and van de Calseyde⁸ used the Goldzieher test meal and routine to study the problem, but based their measure of SDA on a total caloric output which is apparently obtained more from the second BMR reading than from the difference between the two. They found increased SDA in 7 of their 8 cases of Basedow's disease, in 4 cases of non-toxic goiter, and in 3 cases of toxic nodular goiter. They found a decrease but not to normal after thyroidectomy in 3 cases of Basedow's disease. These experiments, while interesting, are apparently open to serious criticism. In the first place, the number of controls is woefully small—only 3. In the second place, their caloric measure is not a true measure of SDA but depends as much on the value of the first BMR as the increase after the test meal.

In view of the considerable discrepancies in the values of the SDA of protein in thyroid disease as reported by various observers, it was felt that there was much in the problem still to be elucidated. On an *a priori* basis, the thyroid gland, whose function is so intimately correlated with the BMR, should play a rôle in the production of the SDA, even though there is admittedly a lack of evidence to support such a view. If such a relationship existed it would give a measure of the ability of the thyroid to respond to stimuli, *i. e.*, the test meal, as well as its ability to function under static, basal conditions.

The histologic finding of marked acinar overgrowth in some thyroid glands, unassociated with marked clinical evidence of any toxicity, suggests the possibility of the clinical entity of a thyroid of borderline pathology able to function well under basal conditions, but perhaps unable to respond normally to an external stimulus, like possibly a protein meal. Such an organ might be analogous to the pancreas of a non-diabetic patient who has nevertheless an abnormal glucose tolerance test. In evaluating the response in metabolism to a test meal it was felt that the time element might be just as important as the quantitative response, *i. e.*, a delayed or hastened reaction might be just as significant as an increased or decreased one.

In choosing a test meal, the small protein meal of Goldzieher was deemed unsatisfactory for two reasons: (1) the possible rôle that the caffeine in the tea might play,⁹ and (2) the consideration that

the increment in BMR, which in normals averaged only about 13%, might not prove to be sufficiently great to give statistically significant differences with as coarse an instrument as the basal metabolism machine. In fact, Goldzieher⁶ reported an average increment of 13% in his normal patients and 13.8% in his group with thyroid diseases. If a large protein test meal were to be used, it would be most important to have an adequate number of controls and to avoid the unreliability of a single sample reading after the test meal as a measure of SDA.

Accordingly, a large protein meal, as exclusively protein as possible, was devised. The meal consists of 100 gm. of commercial gelatin* dissolved in 2 bowls of hot chicken broth, and 175 gm. of white meat of chicken. The gelatin used was guaranteed by the company to contain 85% to 87% pure gelatin, and a nitrogen figure for a sample tested in our laboratory checked with that figure. White meat of chicken is somewhat variable in content but approximates 21% protein and 3% fat.² The total food value of the meal is approximately 123 gm. of protein and 5 gm. of fat.

To determine a measure of the SDA our subjects, following at least 12 hours abstinence from food and at complete rest for at least 1 hour, were given a preliminary basal metabolism test. Immediately thereafter they ate the test meal. Then 3, 5 and 7 hours after the first BMR successive "basal" metabolic tests were made. These latter tests were approximately $2\frac{1}{2}$, $4\frac{1}{2}$ and $6\frac{1}{2}$ hours after the meal. The patients were at complete rest for 1 hour preceding each of these latter tests. At other times during the day they were allowed to move about freely and drink freely, but have no other food or drugs until after the last reading. All patients used in the experiments had had previous BMR's which agreed within a few points with the first BMR of the test. No test was considered satisfactory unless the patient had promptly consumed nine-tenths of the test meal.

With these restrictions our data consist of 55 series of metabolic readings on 45 patients, 44 of whom were from the wards of Mt. Sinai Hospital of Philadelphia and 1 was an out-patient. For the majority of tests a Sanborn water basal metabolism machine was used, and for a few a Jones waterless machine was used. The same machine was used for all tests in any given series.

A preliminary experiment consisted in taking the 4 metabolism readings on 2 patients, 1 normal and 1 thyrotoxic, subjected to all the above restrictions but not given any test meal. In each series there was a variation of at most -5%, indicating that disturbances in the wards were insufficient to affect materially the metabolic reading throughout the day.

Our group of normal controls showed a wide variation in BMR— from -27% to +34%. However, from a careful clinical and

* Kindly donated by the Knox Gelatine Company.

laboratory study of these patients they were found to have no metabolic complaints, and the abnormal BMR's were due not to primary endocrine or metabolic imbalance but rather to causes incident to their illnesses. Thus the low BMR's were due most likely to the low metabolism of convalescence, and the high ones due probably to residual, afebrile inflammations which could easily account for the change.³

On the other hand, the SDA curves from the members of this group showed close agreement. As can be seen from Figure 1, all the curves have similar shapes—all values are increased over the first BMR, the peak is reached in the 3- or 5-hour period, and there-

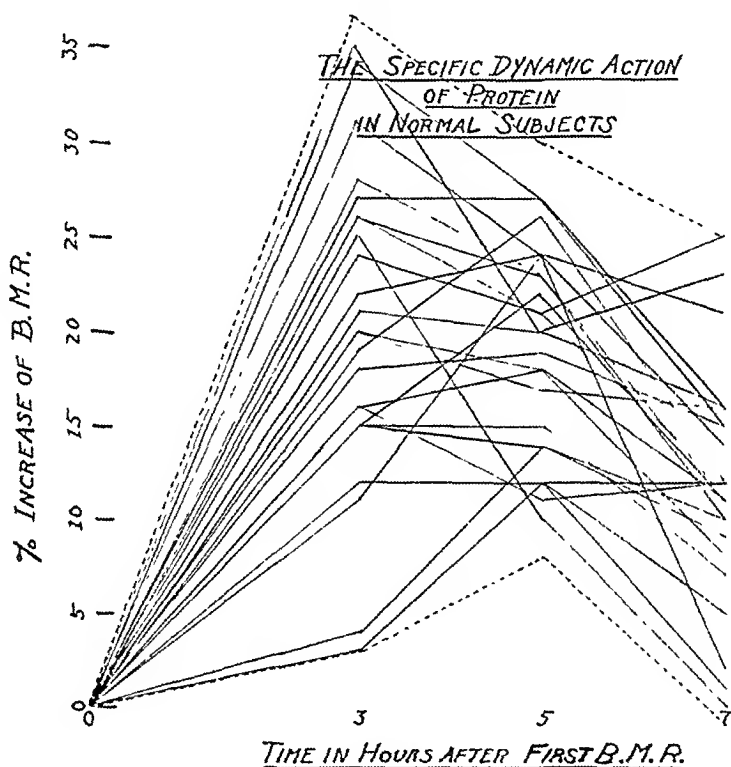


FIG. 1

after the curves either go down or remain relatively constant. The widest variation in values is at the 3-hour period, and there is much closer agreement at the 5- and 7-hour periods. The average value at the 3-hour period is +20, at the 5-hour period +19 and at the 7-hour period +12. The ordinary statistical limits of normal variation, of + or - twice the standard deviation,⁵ at the 3-, 5- and 7-hour periods are respectively from 3 to 37, 8 to 30 and 1 to 25. These limits of normality are shown graphically in Figure 1 as the two dotted lines. The chances are less than 1 in 20 that by mere chance any one value in a normal SDA curve will lie outside these limits in either direction, and less than 1 in 40 that it will lie above the upper limits.

In 3 of these patients repeat SDA tests were made, and the repeat curves were found to agree very closely with the originals.

In general the SDA curves in this group with the highest peaks were found to come from the patients with the lowest BMR's. The line of regression, as shown in the spot chart Figure 2, is slightly down, but not significantly so. These results are in agreement with the findings of Baldwin and Shaw,¹ who found a definite negative correlation between BMR and SDA in 20 unselected patients.

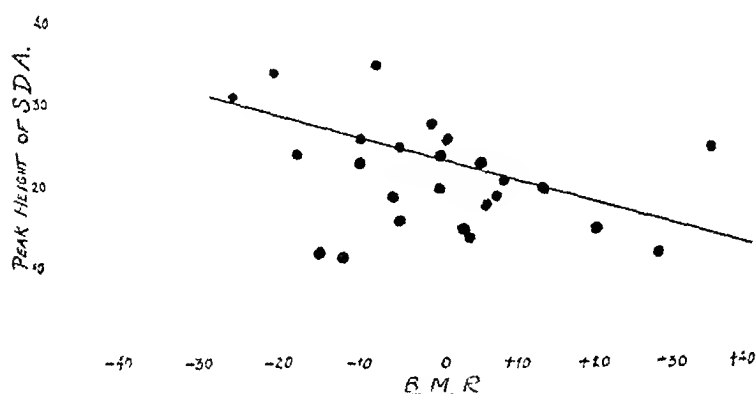


FIG. 2—Spot chart

Our next group is 1 of 11 patients with thyroid disease who had SDA curves with one or more points outside the normal range. When these curves are examined in Figure 3, it is seen that they do not comprise a statistically uniform group like those from normal patients. The curves have their peaks at different times and there is a great deal of variability at each of the time intervals. The curves individually show a tendency to have their peaks not only higher than normal but also later than normal. In each case there is at least one point outside the normal limits. The chance of a normal curve attaining a peak value of as much as 34 at the 7-hour period, as in the curve of A. T., is about 1 in 5000. And even the chance of normally attaining a value of 34 at the 5-hour period, as in the curve of A. G., is less than 1 in 100. Moreover, the high peaks in our normals, as mentioned above, came from patients with low BMR's, whereas the patients in this group all had normal or high BMR's.

Of the 11 patients in this group, 9 had definite clinical diagnoses of hyperthyroidism, either from toxic nodular or toxic diffuse goiter. Seven of them were operated on and the diagnosis proved by surgical specimen. Of these, the most toxic at the time of the SDA test were A. T., R. C. and S. G. all of whom had curves still rising at the 7-hour period. In this group the most abnormal curves were obtained from the most toxic patients, and the most nearly normal

curves were obtained from the patients showing least evidence of hyperfunction and toxicity.

The other 2 patients in this group, A. G. and H. D., had no definite clinical diagnoses of hyperthyroidism. A. G. had a normal

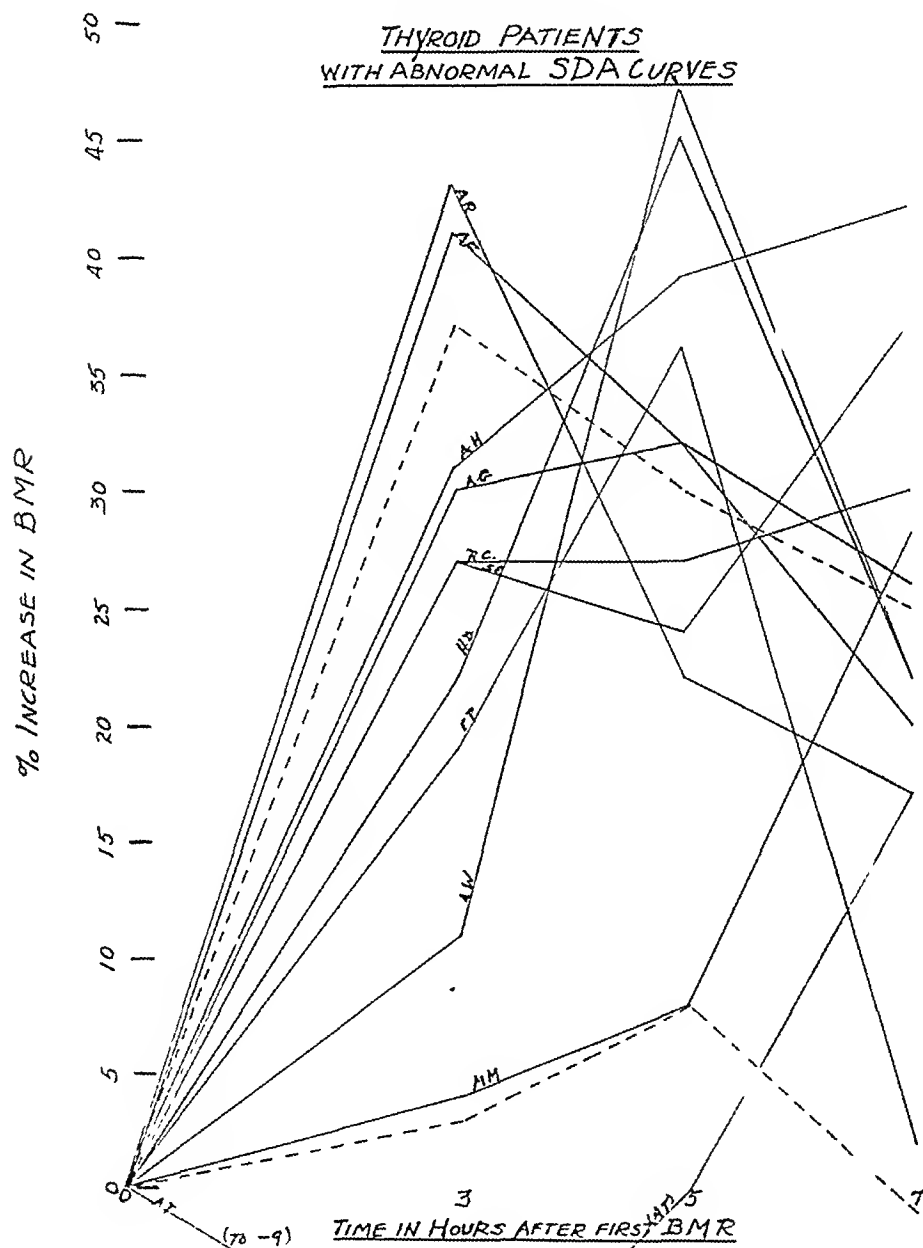


FIG. 3

BMR and thyroidectomy was performed chiefly for obstructive symptoms. On histologic examination, however, her thyroid was found to contain a fetal adenoma showing excessive papillary overgrowth of acinar cells. Hertzler¹⁰ feels that structural changes of this sort are concomitant with changes of function, although this

view is not universal among pathologists. The other patient, H. D., evidenced weight loss, palpitation, coarse tremors, excessive emotional instability and other clinical symptoms of hyperthyroidism. Her galactose tolerance curve peak was 30.3 in the doubtful zone. Her BMR's in the hospital were +32 and +48. However, she had had an occasional normal BMR and, therefore, a definite diagnosis

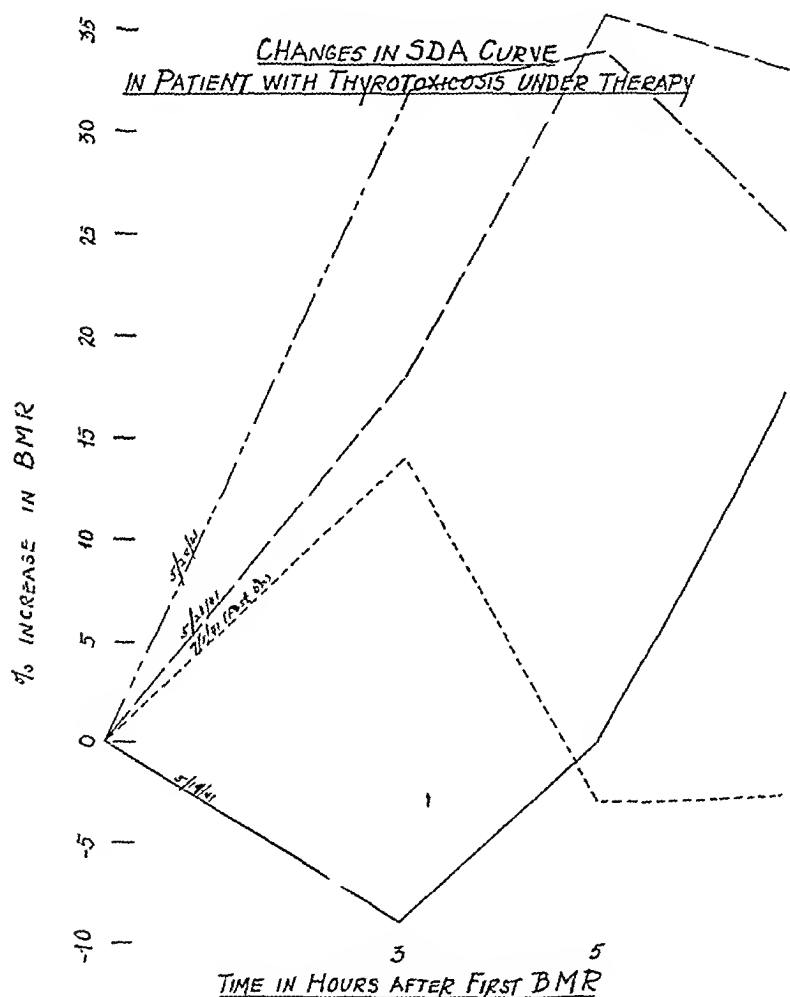


FIG. 4

of hyperthyroidism was not made. In both these cases it was felt that the abnormal SDA curve was an evidence of incipient or transient hyperthyroidism not diagnosable by other laboratory means.

Of great interest was the change in the SDA curves of some of these patients as their thyrotoxicosis improved preoperatively, under iodine and sedative treatment, and after thyroidectomy.

A complete series is that of A. T., consisting of 4 SDA curves, 3 on successive weeks preoperatively and one 2 weeks postoperative. The curves of A. T., shown in Figure 4, change from the first curve, grossly abnormal both as to values and shape, to curves progressively more normal until the postoperative curve is within normal limits. That this sort of progression is not a manifestation of learning ability is shown by the relative stability of repeat SDA curves on C. D., a normal patient, and on F. L., a patient with severe liver damage unaffected by treatment. The curves of 2 other thyrotoxic patients also show a definite change toward normal values after treatment.

THE SDA OF PROTEIN IN
CURED CASES OF THYROTOXICOSIS

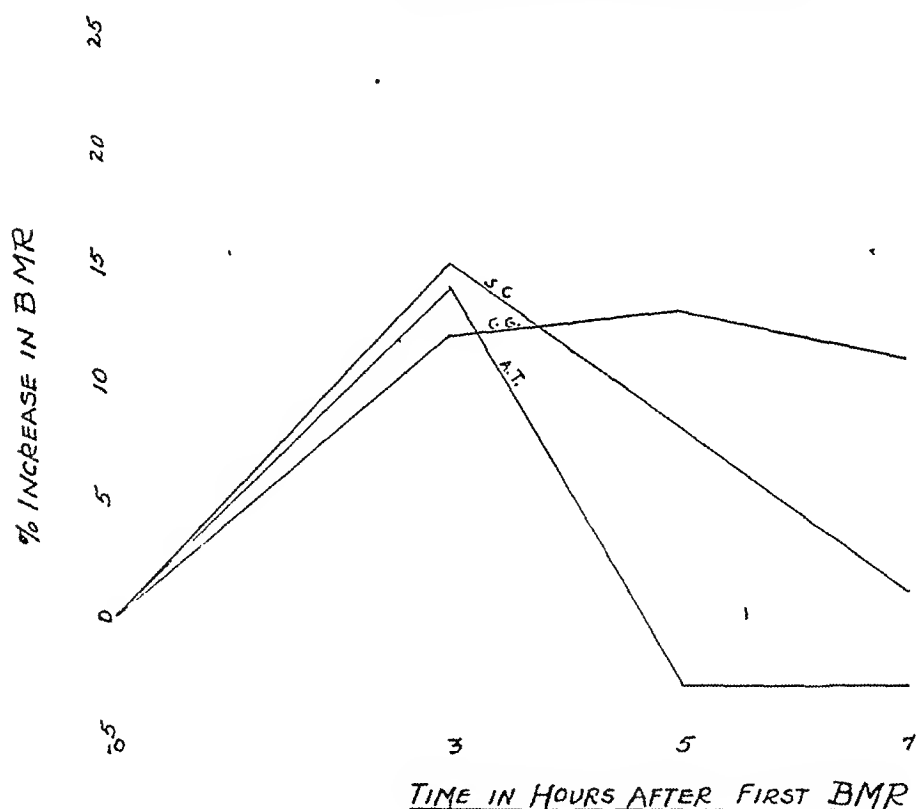


FIG. 5

In keeping with the change toward normal of the SDA as thyrotoxicosis is brought under control are findings of essentially normal SDA curves in 3 patients with cured hyperthyroidism. Their SDA curves are shown in Figure 5 and have normal configurations although the values are in a low normal range. All 3 of these patients had thyroidectomy some years before their present admission, and in addition 1 had irradiation for a reëxacerbation of symptoms.

Our 3 other patients with non-toxic thyroid disease had normal SDA curves, as shown in Figure 6. One patient, H. S., had had a

total thyroidectomy for cardiac disease with a resultant BMR of -28 and an SDA curve of rather low amplitude. The other 2 had non-toxic goiters, although 1, A. C., was a diagnostic problem. She had a BMR of $+46$ and manifested considerable weight loss, palpitation and excessive sweating. However, her thyroid was only minimally enlarged; a galactose tolerance curve reached a normal peak of 20.4, and psychic investigation justified a final diagnosis of anxiety state. After psychotherapy her BMR decreased to $+16$. In this case we feel that the normal SDA curve was a laboratory indication that this patient's symptomatology and elevated BMR were not due to hyperthyroidism.

THE SDA OF PROTEIN IN THYROID PATIENTS
WITH CURVES WITHIN NORMAL LIMITS

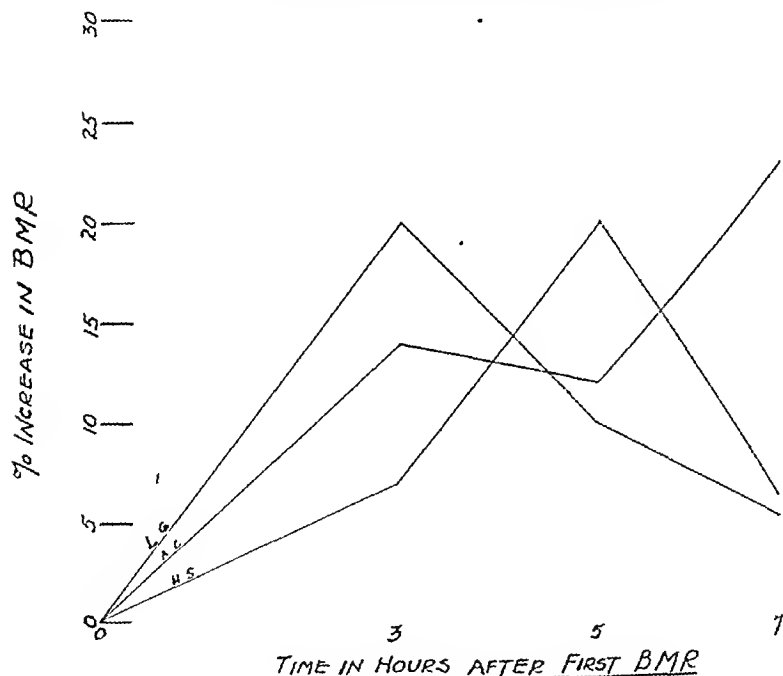


FIG. 6

The final group of SDA curves, shown in Figure 7, was especially interesting because no report could be found in the literature of SDA tests on subjects with the diseases of the 4 patients in this group. In common they demonstrated liver disease and abnormally high blood cholesterol values. Minor liver damage alone, such as that associated with non-obstructive cholecystitis, is insufficient to affect the SDA, for there were several patients in our normal group

with such gall bladder disease. So perhaps the added factor associated with the change in blood cholesterol may contribute in the production of the abnormal SDA in these cases.

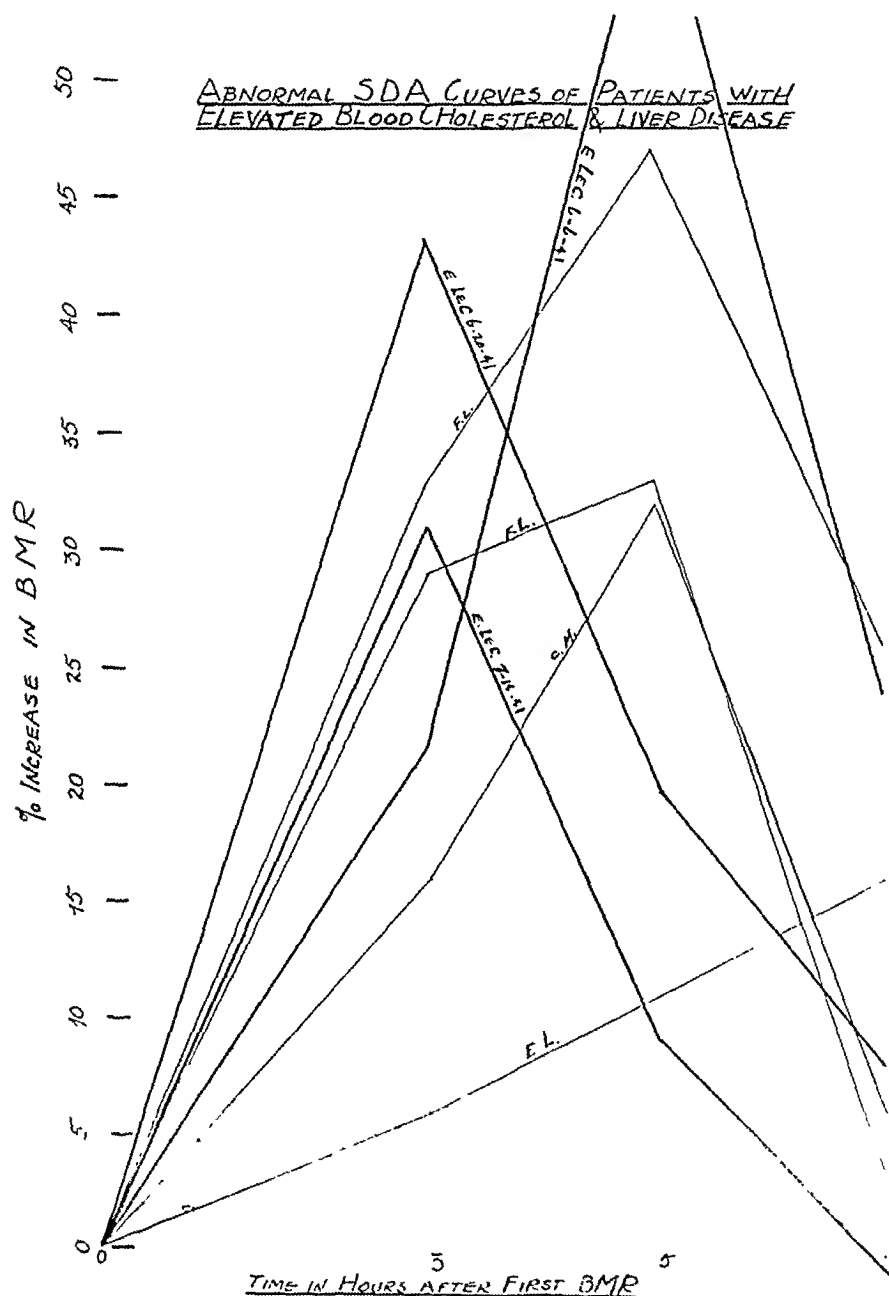


FIG. 7

The patient E. L. had a very severe, fatal liver cirrhosis and a blood cholesterol only moderately elevated. The other 3 patients had very high blood cholesterol values. C. M. was a case of obstructive jaundice and had a blood cholesterol of about 500. F. L. was a case with generalized pigmentation of unknown etiology

associated with a blood cholesterol persistently about 700. Biopsy of liver and lymph node showed severe liver cirrhosis and reticulo-endothelial cell proliferation, respectively. E. LeC. was a patient with xanthomatosis, proven by biopsy, and had no clinical liver disease, but must have had some of the usual liver involvement associated with xanthomatosis. Her 3 curves on 6/6, 6/20 and 7/14 are correlated with the decrease under treatment of her blood cholesterol from about 800 to 600 to 400 respectively. The change in shape and amplitude of her curves to normal limits is very obvious.

According to Thannhauser,¹² the value of the blood cholesterol is a reflection of the activity of the reticulo-endothelial system. Moreover, the liver is the greatest reservoir of reticulo-endothelial cells in the body. The obvious hypothesis, therefore, suggested by this group of cases is that the SDA is in some way mediated through the reticulo-endothelial system.

Summary. 1. Using a high protein test meal of chicken and gelatin, a technique of obtaining the SDA of protein has been described where the measure of the SDA has been the curve of 4 basal metabolic readings taken respectively immediately before the test meal and 3, 5 and 7 hours later. Forty-five subjects were used and single or multiple SDA tests performed on each.

2. On 25 patients, normal as regards absence of endocrine and metabolic dysfunction, essentially similar SDA curves were obtained and limits of statistical normality calculated. In these patients the peak was reached in the third to fifth hour. The highest peaks were found in those patients with the lowest BMR's.

3. In 11 patients with hyperthyroid disease, proven or strongly suggested, single and multiple SDA curves had points significantly higher than normal levels. In those patients with excessive toxicity the SDA curves tend to have their peaks shifted to the right. In 2 of the cases with only possible borderline hyperthyroidism the SDA was the only definitely abnormal laboratory finding. In 3 of the most toxic patients the SDA curves approached normal limits as the toxicity decreased under treatment.

4. In 3 cases of postoperative cured hyperthyroidism and in 3 other cases of non-toxic thyroid disease the SDA curves were normal.

5. In 4 patients with varied diseases all evidencing some liver damage and elevated blood cholesterol, 2 of whom also had biopsy evidence of reticulo-endothelial cell proliferation, abnormal SDA curves were obtained. Of this group the abnormally elevated curves of the patient with xanthomatosis approached normal as the blood cholesterol level decreased toward normal. Therefore, the reticulo-endothelial system may be involved in the production of the SDA of protein.

Conclusion. It is felt that the method of determining the SDA of protein, as described in this paper, may be of value in diagnosing

borderline cases of hyperthyroidism, and in determining the course of hyperthyroidism for appraisal of the most opportune time for operation.

We should like to acknowledge gratefully the help of Dr. David Meranze in offering constructive criticisms of these experiments and making available the laboratory facilities for this work, and to Misses Gallant, Miller and Shapiro for making a number of the tests. We wish to thank also the Dietary Department for preparing the test meals and the Knox Gelatine Company for donating the gelatin used.

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BOOK REVIEWS AND NOTICES

ATLAS OF OPHTHALMIC PATHOLOGY. By ELBERT DeCOURSEY, Major in the Medical Corps of the U. S. Army; Formerly Pathologist to the Registry; and J. E. ASH, Colonel, M. C., A. U. S., Curator, Army Medical Museum; ROY M. REEVE, Photographer; HELEN CAMPBELL WILDER, Microscopist; LAWRENCE P. AMBROGI, Technician. Prepared at the Army Medical Museum, Office of the Surgeon-General of the U. S. Army, from material in the Registry of Ophthalmic Pathology. Third Edition, revised. Pp. 136; profusely illustrated. Omaha: Amer. Acad. of Ophthalmology and Otolaryngology, 1942. Price, \$5.00.

ATLAS OF DENTAL AND ORAL PATHOLOGY. By JOSEPH L. BERNIER, Major in the Dental Corps of the U. S. Army, Pathologist to the Registry; JAMES B. MANN, Colonel in D. C., A. U. S., Formerly Pathologist to the Registry; J. E. ASH, Colonel, M. C., A. U. S., Curator. Prepared at the Army Medical Museum, Office of the Surgeon-General, from material in the Registry of Dental and Oral Pathology. Second Edition, revised. Pp. 178; profusely illustrated. Chicago: Am. Dental Assn., 1942. Price, \$5.00.

ATLAS OF OTOLARYNGIC PATHOLOGY. By J. E. ASH, Colonel, M. C., A. U. S., Curator, with the assistance of J. L. BERNIER, Captain, D. C., A. U. S., Assistant Pathologist; ROY M. REEVE, Photographer. Prepared at the Army Medical Museum, Office of the Surgeon-General of the U. S. Army, largely from material in the Registry of Otolaryngic Pathology. Third Edition, revised. Pp. 173; profusely illustrated. Omaha: Amer. Acad. of Ophthalmology and Otolaryngology, 1942. Price, \$5.00.

THESE atlases have an unusual aim and occupy an unusual position among pathology publications. The Atlas of Ophthalmic Pathology and that of Otolaryngic Pathology "are the outgrowth of the syllabus which was prepared to accompany the loan set of slides on [Ophthalmic and] Otolaryngic Pathology." They were sponsored by the American Academy of Ophthalmology and Otolaryngology, which has adopted them as texts for . . . Study. The Atlas of Dental and Oral Pathology was prepared under the authorization of the American Dental Association.

The material is arranged, as previously, primarily as "atlases of morphologic pathology with only incidental allusion to clinical aspects and to treatment and the attempt has been made to present the material as an adaptation of the general principles of pathology to the special fields."

In the Ophthalmic Atlas, with 136 pages of text, each accompanied by one or more full pages of photomicrographic illustrations, many different lesions of the eye are treated. One gets some idea of the value of the material, both for instruction and for comparative reference, by perusal of the parallel columns of Index, where, for example, some 40 different kinds of tumors are listed. The slightly larger Atlas of Otolaryngic Pathology presents equally valuable material. One might search long without finding case abstracts and photographs of mastoid cholesteatoma, various congenital defects of the middle and internal ear, xanthoma, amyloid tumor, leprosy, blastomycosis of larynx and so on. In the Atlas of Dental and Oral Pathology, a "rather complete revision" has been made. New cases have been added, also several conditions affecting the pharynx, several pages on dental histology, gas gangrene, and several blood pictures, for good measure.

We agree heartily with all that Colonel Ash has to say about the status of pathology in medicine and about the desirability of specialist clinicians having thorough knowledge of pathology and of other basic sciences. We hope that the aims of the sponsors and the labors of the producers will be properly rewarded by the use that the Atlases are put to by the members of the respective associations. Even if the reward is inadequate in this respect, however, the material is sufficiently ample and detailed to be of great use to general and special pathologists of any land. The illustrations in their half-tone reproductions are almost as good as in their previous form, and the liberal use of key letters referred to in the text makes them easily legible by the reader.

E. K.

MANUAL OF DERMATOLOGY. MILITARY MEDICAL MANUALS NATIONAL RESEARCH COUNCIL. By DONALD M. PILLSBURY, M.D., MARION B. SULZBERGER, M.D., and CLARENCE S. LIVINGOOD, M.D. Pp. 421; 109 illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, \$2.00.

This volume is one of a series developed to furnish the medical departments of the United States Army and Navy with compact presentations of necessary information in the field of military medicine.

The diagnosis and treatment of the common skin diseases affecting persons of the age-sex group in the armed forces are briefly discussed. The first 166 pages are devoted to practical directions for use of the manual; diagnosis based on the primary and secondary lesions and on the history; principles of local treatment. It appears to the Reviewer that reduction of the unusually large size of the illustrations and of the wide type in printing could have been utilized in discussion of some of the common skin diseases without increasing the number of pages.

In the formulary, there are preparations such as vioform powder, anthralin, sodium lauryl sulfate, chlorhydroxy-quinolines, that are not well known except to dermatologists. The formulary also includes recently developed insecticides, the use of which the authors state they have had no experience. It is doubtful if some of the 11 instruments in Figure 109 are ever used except by the dermatologist.

J. K.

THE VARIETIES OF TEMPERAMENT. By WILLIAM H. SHELDON, Ph.D., M.D., Department of Psychology, Harvard University, and S. S. STEVENS, M.D., Harvard University. Pp. 520; 7 figures. New York and London: Harper & Brothers, 1942. Price, \$4.50.

In this volume the author makes use of a frame of reference for morphologic description of the human physique which he has already established in a previous volume, *Variety of Human Physique*. This frame of reference consists of three fundamental types of physique or somatotypes, namely, endomorphic, mesomorphic, and ectomorphic.

The present volume deals with *Temperament* as a part of the fundamental dynamics of human personality. The *Temperament* is described as that "level of personality just above physiological function and below acquired attitudes and beliefs—it is the level where basic patterns of motivation manifest themselves." The author in the first part of the book describes how from a list of 6250 "traits" of human beings he selected 60 fundamental ones which he used in a study of 200 young men. This study was carried out by morphologic analysis together with the "trait" analysis in a series of 20 analytical interviews for each subject extending through an academic

year. During the interviews a physical and health history—genetic and family history, economic, social, sexual, educational and æsthetic histories were taken, as well as noting characteristic traits and habits, and in special cases, when necessary, resorting to free-association and even to dream analysis. He then presents a detailed report of the 200 individual cases. In the latter part of the book he discusses the tentative conclusions which in brief are—the 60 traits can be divided in three groups of 20 and these three groups in turn correlated with the morphologic types in the order of ± 0.80 . The theoretical considerations put forth are quite interesting and illuminating.

It should be stressed that the author is careful to point out that this method of study of "constitutional psychology" as described by him is at the present time only of value as a method of investigation in the hands of those people who have been trained in "constitutional psychology." This entails obtaining graduate psychology work, a degree in medicine as well as at least a year's training in this particular method, after which the individual preferably should receive a year's training in a psychiatric institution as well as an adequate period of psychoanalysis. O. R.

BLOOD SUBSTITUTES AND BLOOD TRANSFUSION. Edited by STUART MUDD, M.A., M.D., Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and WILLIAM THALHIMER, M.D., Director, Human Serum Division, Public Health Research Institute of the City of New York, Inc. Pp. 407; 94 figures. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

THIS book, a symposium monograph, is the product of 77 authors whose contributions were presented, and of those who discussed these contributions at the annual meeting of the American Human Serum Association, held in Cleveland on June 2 and 3, 1941. In many instances the results of work subsequent to the association meeting have been introduced by the authors. The 38 chapters, each of which constitutes a separate contribution, are divided into 7 sections, whose titles in the order of arrangement are: Etiology and Mechanisms of Secondary Shock; Methods of Preservation of Plasma and Serum by Desiccation and by Freezing; Hemoglobin, Serum Albumin and Casein Digest as Blood Substitutes; Blood Substitutes in the World Emergency; Whole Blood: Storage, Transportation, Administration, Isoagglutinins and Blood Group Specific Substances; Therapeutic Experiences with Serum and Plasma; and a "recapitulation and outlook" by Dr. Mudd.

Thus, we find an analysis of the mechanisms of secondary shock leading to the generalization that the basic physiologic defect is reduced circulating fluid volume. The many questions relating to procurement, preservation, administration and efficacy of human serum and plasma are presented and discussed in detail. Experiments with other blood substitutes, human hemoglobin and human and bovine serum albumin, are described. Aspects of the storage, transportation, and administration of whole blood are included. The wartime application of this very vital subject is presented. Each contribution is usually followed with a substantial number of references.

The assembling of this material into a handy volume comes at a very useful time in view of the many and relatively recent advances in this field, the rather widespread establishment of blood banks in hospitals, and the great impetus given by the belligerent nations. This book is a well-recommended volume for both the investigator and clinician working in the field of "blood substitutes and blood transfusions." M. T.

MORRIS' HUMAN ANATOMY: A COMPLETE SYSTEMATIC TREATISE. Edited by J. PARSONS SCHAEFFER, A.M., M.D., Ph.D., Sc.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia. Tenth Edition. Pp. 1635; 1155 illustrations. Philadelphia: The Blakiston Company, 1942. Price, \$12.00.

PROFESSOR SCHAEFFER, the new editor of this book, has replaced Prof. C. M. Jackson, who has withdrawn due to illness; however, the latter continues to be a contributor in collaboration with Prof. R. F. Blount, now of the University of Texas. Other new contributors and their sections are as follows: J. C. B. Grant (Univ. of Toronto), the musculature; B. M. Patten (Univ. of Michigan), the cardiovascular system; H. Cummins (Tulane Univ.), the skin and mammary glands; Olof Larsell (Univ. of Oregon), the nervous system. Death has removed Professors Bardeen, Sr., and Stockard as contributors, and Professor Hardesty has retired from active participation.

In the present edition the printed page is both longer and wider, making it possible to set more of the fundamental text matter in the larger type, without increasing significantly the number of pages, and thus adding to ease of reading. Use of smaller type has been continued for items of special interest; but a considerable amount of the former small print has been changed to larger size. Significantly, many new and better illustrations have replaced former ones, and this is particularly true in the sections on development and the cardiovascular system. The Reviewer is sorry to note that many of the cross-section illustrations have been dropped from the section on musculature. It is apparent that most of the sections have been revised or rewritten to varying degrees. The section on developmental anatomy is presented in an entirely new fashion, dealing more with the body as a whole, rather than devoting space to the different systems. This is a particularly good presentation in a textbook of anatomy. Some of the sections show relatively little change—one containing exactly the same bibliography as found in the previous edition. The Editor is to be congratulated on his very comprehensive and useful index, which required 118 pages. This definitely increases the value of the work, both as a student's textbook and as a reference book. As a whole, the changes made in this edition justify its revision, and it should enjoy a continued increasing popularity.

M. T.

OSLER'S PRINCIPLES AND PRACTICE OF MEDICINE. Originally written by SIR WILLIAM OSLER, BART., M.D., F.R.C.P., F.R.S. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Hon. Sc.D., Hon. F.R.C.P. (CAN.). F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital; Visiting Physician, Beth Israel Hospital, Boston. Fourteenth Edition. Pp. 1500; some tables and figures. New York: D. Appleton-Century Company, 1942. Price, \$9.50.

THE delight with which English-speaking physicians delved into the first edition of Osler, with its freshness of vision, first-hand content of material, unhackneyed text, and breezy often anecdotal phraseology, can be recalled by many who now welcome this semicentennial edition, the second to be produced by Dr. Christian, after Thomas McCrae had revised three. The almost constantly triennial appearance of a new edition through these 50 years is sufficient in itself to brand this the greatest of modern textbooks of medicine.

Comparison of this 14th with the 1st edition at once brings out two facts: how much all branches of internal medicine have progressed in 50 years,

and how well the three editors have demonstrated that good adaptation is rewarded by success, as well as being necessary for survival. In the course of 13 editions, the arrangement as well as the content of material has been greatly changed. The classification of diseases by etiology, which at first occupied about one-third of the text in different parts of the volume, now requires one-half of the space and withdraws such diseases as the pneumonias and rheumatic fever from their former positions in the respiratory and constitutional sections into infectious diseases. The number of new conditions, even new sections (such as diseases due to viruses, rickettsias, deficiency and endocrine disease) is large and to be expected. Instead of 6 "Infectious Diseases of Doubtful Nature," we now find 14, though knowledge of Onyala, Big Heel, Barcoo and others may not be vitally necessary to most users of the book.

Many sections still retain their historical paragraphs and characteristic Oslerian touches. Though one would have greater difficulty today in preparing a set of non-medical examination questions from the 14th than from the 1st edition, the younger Aphrodite still appears and Plato still influences, and v. Helmont's bloody Moloch still warns against excessive bleeding (p. 61). Pepper (Secundus), H. C. Wood and Palmer Howard are still included in the story of pernicious anemia.

To indicate the many improvements in the present edition is beyond our scope. The everincreasing speed of medical progress, especially in the field of treatment, has required unusual labor for the new edition. The increased number of references at the end of each chapter reflects this situation, which Dr. Christian's retirement from teaching and hospital work undoubtedly helped him to meet. He is to be most warmly congratulated on the success with which he has "changed the text to fit recent advances in medicine and yet has preserved that spirit of the past editions, which has seemed to fill so well the needs of students and practitioners." E. K.

CLINICAL ANESTHESIA. By JOHN S. LUNDY, B.A., M.D., Head of Section on Anesthesia, Mayo Clinic; Professor of Anesthesia, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota; Diplomate and Member of the American Board of Anesthesiology, Inc.; Member of the Subcommittee on Anesthesia, National Research Council. Pp. 771; 266 illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, \$9.00.

THIS is an extremely difficult book to review. The author's purpose in writing it is "to describe most of the methods of anesthesia that I regularly employ and some that I use only occasionally." The result is necessarily not an inclusive coverage of clinical anesthesia as the title implies, but an account of anesthesia practices at the Mayo Clinic. A tremendous amount of work has been done by Dr. Lundy and it is this vast experience which he outlines.

Some advantages accrue from this type of presentation. For example, regional anesthesia—a strong point at Rochester since 1920—is admirably discussed. Furthermore, there is a certain benefit to be derived from the consideration of an individual's particular beliefs, likes, and dislikes; and since this is essentially an individual presentation, the reader has this opportunity here.

The volume does not lend itself readily to reading, probably because of loose organization. A laudable attempt has been made in presenting a section on Choice of Anesthetics. There is no comprehensive bibliography. In all fairness to the author it should be pointed out that these omissions may be intentional, since they are recognized in the foreword.

R. D.

SURGICAL PATHOLOGY. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology, University of Toronto. Fifth Edition. Pp. 843; 502 illustrations, 16 colored plates. Philadelphia: W. B. Saunders Company, 1942. Price, \$10.00.

Good textbooks of surgical pathology in English are considerably rarer than those on General and Special Pathology. Many advances have been made in the 4 years since the 4th edition of this work appeared, so that this edition is timely as well as generally desirable.

In Thoracic Pathology, progress has been so great that a new chapter has had to be added, and it is a good one. Other new subject matter includes: "head injuries, wound infections, anaërobic streptococcal infections of the skin, burns, dermatofibroma, Hurthle-cell tumor, duodenitis, chronic ulcerative colitis, liver death (*i. e.*, sudden death during operation on the liver—Ed.), bile peritonitis, pyelonephritis in relation to arterial hypertension, acid phosphatase in carcinoma of the prostate, interstitial endometrioma, plasma cell mastitis, fibrosing adenomatosis of the breast, osteomyelitis of the frontal bone, Arnold-Chiari malformation, skeletal lipoid granulomatosis, injuries, and tumors of nerves, synovial sarcoma, Ollier's disease, Morquio's disease, osteoid-osteoma, reticulum cell sarcoma, liposarcoma, and eosinophilic granuloma of bone."

The references at the end of each chapter, now advisedly classified according to subject, have been usefully amplified. E. K.

INTRODUCTION TO THE PSYCHOANALYTIC THEORY OF THE LIBIDO. By RICHARD STERBA. Nervous and Mental Disease Monograph, No. 68. Pp. 81. New York: Nervous and Mental Disease Monographs, 1942. Price, \$2.00.

THE author protests against those analysts who refuse to acknowledge Freud's theory of the instincts, wherein they are considered as active stimuli that come from within the body and flow into the psyche. The master told of two large groups of instincts that are antagonistic—those concerned with self-preservation and those of sexuality. In Freudian psychology, the libido is concerned solely with sexual pleasure and desire, and its development in the child is here considered in the following order: first and second oral phases; first and second anal phases; sadism and masochism; the genital phase; the latency period and puberty. It is stated that those who practice perversions, or indulge in fantasies pertaining thereto, would include half of mankind. Doubtless the true analyst followers of Freud will approve of much that this monograph offers.

N. Y.

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY. Edited and Revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. (B'HAM), Jodrell Professor of Physiology in University College, London. Chapters on the Special Senses Revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S., Professor of Physiology at St. Bartholomew's Medical College. Eighth Edition. Pp. 1257; 673 figures. Philadelphia: Lea & Febiger, 1942. Price, \$10.00.

THE 8th edition of Starling has been revised, partly rewritten and new material added, in accordance with changes in viewpoint and advancement in knowledge of the subject material. As in the previous editions, certain biochemical aspects of physiology are included and well presented. References are given in footnotes and at the end of each section.

Always an excellent text in human physiology, this modern edition maintains and adds to the virtues of its predecessors. While the specialist in any given field of physiology might differ in some details with the point of view presented, on the whole the subject material is eminently sound, well selected and clearly presented, and free of involved controversial discussions which confuse the student. It is in fact what it is intended to be a scientific presentation of the principles of human physiology without stress on the clinical application, as in some recent texts for medical students.

The choice between these two types of texts in medical teaching must rest in the first instance upon the soundness and adequacy of the presentation of the fundamental principles of physiology. S. G.

FUNDAMENTALS OF PSYCHIATRY. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department, Undergraduate School of Medicine, University of Pennsylvania; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Psychopathic Division, Philadelphia General Hospital. Pp. 201; 15 figures. Philadelphia: J. B. Lippincott Company, 1942. Price, \$3.00.

BELIEVING that in the present world crisis it is imperative that some psychiatric knowledge be available for physicians in civil and military life, the author offers this manual to supply that need. There are important chapters on Etiology, Classification of Mental Diseases, Methods of Examination and Symptoms, Organic Psychoses, Functional Psychoses and Psychoneuroses, and The Psychiatry of War. This last chapter discusses the impact of war, war and the civilian, war and the soldier, and treatment of military neuropsychiatric disabilities.

Some of the more drastic forms of treatment are described, such as prolonged narcosis in the manic reactions and schizophrenia, and the shock treatment, particularly in the latter psychosis; also leukotomy in the prefrontal areas, thereby severing some of the fibers between the ideational and emotional regions. Obviously, only skilled workers should adopt such measures and then only in hospitals fully equipped for such procedures.

Hysteria is discussed as a neurosis, also as a neuropsychosis and psychoneurosis; such a loose use of terms is not in accord even with the dictionary and will prove confusing to the average practitioner. It is enlightening to learn that civilians who seek the deeper bomb-proof shelters show more fear than do those intimately concerned with bombings, such as workers in fire brigades. A relative but not an absolute increase in crime is observed at the present time. The manual is informative and will meet the needs of many critical situations. N. Y.

THE HEMORRHAGIC DISEASES AND THE PHYSIOLOGY OF HEMOSTASIS. By ARMAND J. QUICK, Ph.D., M.D., Associate Professor of Pharmacology, Marquette University School of Medicine, Milwaukee, Wis. Pp. 340; 24 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, \$5.00.

This volume is the most valuable monograph on the hemorrhagic diathesis that has appeared in recent years. The Author's work, much of which has appeared in the pages of this Journal, indicated the true cause of the hemorrhagic tendency in jaundice and paved the way for the treatment of this condition by vitamin K. He is not only a distinguished investigator but a very able writer.

The presentation of the history and physiology of blood coagulation in the opening chapters of the book makes one of the most complicated subjects in medicine remarkably clear and understandable. This comprises a

very valuable portion of the book. The subject of blood coagulation is perhaps one of the most under-emphasized aspects in the whole realm of medicine and Dr. Quick's monograph, coming soon after an important series of advances had been made, should be very profitable reading for physicians and physiologists alike.

J. R.

A TEXTBOOK OF FRACTURES AND DISLOCATIONS COVERING THEIR PATHOLOGY, DIAGNOSIS, AND TREATMENT. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Surgery (Rush) of the University of Illinois; Attending Surgeon, Presbyterian Hospital; Formerly Attending Surgeon, Cook County Hospital, Chicago, Ill.; Fellow, American Surgical Association and American Orthopedic Association; Member of the Central Committee on Fractures of the American College of Surgeons; Chairman of the Fracture Exhibit Committee of the Scientific Exhibit of the American Medical Association; Chairman, Chicago Regional Fracture Committee. Fourth Edition. Pp. 1106; 1140 engravings. Philadelphia: Lea & Febiger, 1942. Price, \$12.50.

DR. SPEED's book on fractures is a welcome relief from the current trend toward the edited textbook written by contributors or their assistants. One feels that the book truly presents considered judgments based on long experience in the management of fractures.

Dr. Speed's important position in the surgical profession has undoubtedly provided unusual opportunities for keeping in contact with new developments in fracture treatment in all parts of the country. Many of these newer methods are presented and some of them are recommended.

The same viewpoint, practical recommendations, and the concrete experiences frequently cited combine to make this one of the best reference books on fractures available to student, general practitioner, or surgeon. The book is abundantly illustrated and while the illustrations do not appear to have been revised as thoroughly as the text they are for the most part clear and valuable.

J. R.

ANOXIA. ITS EFFECT ON THE BODY. By EDWARD J. VAN LIERE, PH.D., M.D., Professor of Physiology and Dean, School of Medicine, West Virginia University, Morgantown. Pp. 254; 16 figures and index. Chicago: University of Chicago Press, 1942. Price, \$3.00.

A REVIEW of the literature dealing with this subject is especially opportune now because of the very rapid expansion of interest in problems of aviation, among which anoxia is of course prominent. The Author for many years has had intimate contact with some phases of the anoxia problem and is well qualified for the task of assembling the voluminous, often conflicting, data and opinions. He has done this thoroughly and has included a complete bibliography, so that the book should prove valuable not only to specialists in aviation medicine but also to general practitioners and to students and researchers in physiology.

C. S.

A BIBLIOGRAPHY OF AVIATION MEDICINE. By EBBE CURTIS HOFF and JOHN FARQUHAR FULTON. Prepared for the Committee on Aviation Medicine, Division of Medical Sciences, National Research Council Acting for the Committee on Medical Research, Office of Scientific Research and Development, Washington, D. C. Pp. 237. Springfield, Ill.: Charles C Thomas, 1942. Price, \$4.00.

COMMENT upon a Bibliography gives scarce opportunity for rhetoric upon the part of the Reviewer. But in this case no difficulties arise. Hoff and

Fulton have done a superb job in thoroughness, arrangement, codification, and format. The Bibliography comprises over 6000 references from all sources including extensive quotations from the Russian and the Japanese literature. Altogether some 800 different journals are cited. The arrangements and classification of the author and subject indices comprising thousands of articles is a task in itself. Soon we are coming to the situation where in rapidly developing and expanding fields periodic accumulations of literature references become vital to the expert. The Authors have shown in splendid fashion the way this can be done. W. S.

THE CONQUEST OF BACTERIA (FROM SALVARSAN TO SULFAPYRIDINE). By F. SHERWOOD TAYLOR, with a foreword by HENRY E. SINGER. Pp. 163, with index. New York: Philosophical Library and Alliance Book Corp. Price, \$2.00.

This book is intended for laymen and the first 73 pages contain an interesting and quite adequate account of the perspective of chemotherapy (the development of the germ theory of disease, the defenses of the body, the naturally occurring specific drugs, and the rise of the synthetic drug industry). The remaining pages are devoted to chemotherapy, 70 of them to the sulfonamide group. Pages 111 to 115 contain a description of the operation of the laws of chance in clinical tests of new drugs, and this can be read with profit by most practitioners of medicine. The theme of this book is perhaps the most interesting in current medicine and the Author does it full justice. Unfortunately the viewpoint throughout is that of the English in 1940 and M & B 693 (sulfapyridine) is presented as the nearly perfect solution of problems of chemotherapy; developments between 1940 and the publication date (March, 1942) are not mentioned; sulfathiazole receives brief mention but sulfadiazine and sulfaguanidine do not, and American readers will be left wondering why sulfapyridine is no longer widely used in this country. C. S.

THE CLINICAL APPLICATION OF THE RORSCHACH TEST. By RUTH BOCHNER, M.A., Psychologist, Formerly Bellevue Psychiatric Hospital, and FLORENCE HALPREN, M.A., Psychologist, Bellevue Psychiatric Hospital. Introduction by KARL M. BOWMAN, M.D., University of California Medical School. Pp. 216. New York: Grune & Stratton, 1942. Price, \$3.00.

In 1921, Hermann Rorschach, a psychiatrist, brought forth his psychodiagnostic method test, known as the Rorschach or ink-blot test. The following year, at the age of 38, the brilliant Swiss research worker died. While the subject is of compelling interest to psychiatrists whom it may aid in prognosis and treatment, until the last few years, most of its interpretations of personality have been made by psychologists. Application of this test is through the medium of 10 cards that are standardized copies of ink-blots, so chosen that they may hold suggestive value for the respondent. Symbols representing the complete responses from all 10 cards must be recorded. Following the scoring is a tabulation for the complete record. The relationship of the actual responses from each card, to the total number of responses, is expressed in percentages and is quite a problem. Following the completed scoring comes the interpretation, in which a single factor is never of more than a relative proportion of examiner's interpretation of the 10 card assemblage.

The Authors give actual interpretations from their records of children, adults, mental defectives, neurotics, schizophrenics, and of organic diseases.

The Reviewer regrets the absence of that troublesome and perplexing entity, the psychopathic personality. After indicating the wide ramifications and uses of this technique, the authors admit that numerous important problems are yet unsolved and mention lack of established norms.

Though the volume with its many symbols and interpretations does not lend itself readily to adequate review, it is a valuable and stimulating contribution to the ink-blot test literature. An abundant bibliography is appended but there is no index.

N. Y.

CHEMISTRY AND PHYSIOLOGY OF THE VITAMINS. By H. R. ROSENBERG, Sc.D. Pp. 674; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, \$12.00.

DURING the past 10 years tremendous strides have been made in the development of the chemistry of the vitamins. This monograph brings together, for the first time, a rather detailed summary of these advancements. In addition to the chemistry, considerable space is also given to a discussion of the physiology of the vitamins.

A separate chapter is devoted to each of the known vitamins and the presentation of the subject within each chapter follows a rather definite outline. As an example, the chapter on pantothenic acid is subdivided into the following headings: 1, Nomenclature and Survey; 2, Chronology; 3, Occurrence; 4, Isolation; 5, Properties; 6, Chemical Constitution; 7, Synthesis; 8, Industrial Methods of Preparation; 9, Biogenesis; 10, Specificity; 11, Determination; 12, Standards; 13, Physiology of Plants and Microorganisms; 14, Animal Physiology; 15, Avitaminosis and Hypovitaminosis; 16, Hypervitaminosis; 17, Requirements. The other chapters follow essentially the same outline. In addition to the subjects mentioned above there is a chapter on the unidentified vitamins and one on the "vitagens"—a term used by the author to designate a dietary essential not classed as a vitamin or a mineral. These compounds include the essential fatty acids, the essential amino acids, choline, etc. At the end there is a patent index in which are listed the United States, British, German and French (and a few from other countries) patents dealing with the vitamins.

Unquestionably a great deal of labor has gone into the preparation of this monograph for a vast amount of the literature has been covered. References to the literature are given in footnotes at the bottom of each page. On the whole, the book is well done and supplies a real need especially in respect to the chemistry of the vitamins. It is so written and the subject matter has been so selected and arranged as to be very useful for those whose interest lies in the practical as well as the academic field.

J. J.

BIOLOGICAL SYMPOSIA VOL. IX. SEX HORMONES. Edited by F. C. KOCH, Chairman of the Department of Biochemistry, University of Chicago, and PHILIP E. SMITH, Professor, College of Physicians and Surgeons, Columbia University. Pp. 146; 25 illustrations. Lancaster: The Jacques Cattell Press, 1942. Price, \$2.50.

This book is composed of 8 invitation papers presented in two symposia. The symposium on *Sex Hormones—Their Action and Metabolism* presented at the Fiftieth Anniversary Celebration of the University of Chicago in September 1941, and the symposium on *Hormonal Factors in the Inversion of Sex* presented at the annual meeting of the American Association of Anatomists in April 1942. The titles of the papers describe adequately the phases of the subject which were covered and the names of the participants is sufficient guarantee of the quality of the contributions.

The papers given at the first symposium are as follows: *The comparative biology of testicular and ovarian hormones* (Carl R. Moore, Professor of Zoölogy, University of Chicago); *The comparative metabolic influence of the testicular and ovarian hormones* (A. T. Kenyon, Department of Medicine, University of Chicago); *The metabolism of estrogens* (E. A. Doisy, Professor of Biological Chemistry, St. Louis University); and *The excretion and metabolism of male sex hormones in health and disease* (Prof. F. C. Koch, the Senior Editor).

The papers presented at the second symposium are: *Sex inversion in the plumage of birds* (C. H. Danforth, Professor of Anatomy, Leland Stanford University); *Sex inversion in Amphibia* (R. R. Humphrey, Professor, School of Medicine, University of Buffalo); *Hormonal factors in sex inversion* (Dr. R. R. Greene, Northwestern University Medical School); and *Hormones and the experimental modification of sex in the opossum* (Prof. R. K. Burns, Jr., Department of Embryology, Carnegie Institution).

C. Z.

THE MICROSCOPE. By SIMON HENRY GAGE, Emeritus Professor of Histology and Embryology in Cornell University. Seventeenth Edition. Pp. 617; 313 figures. New York: Comstock Publishing Company, 1942. Price, \$4.00.

THIS classic in scientific literature, far from resting on its laurels, continues its efforts to keep abreast of the times. "Changes have been made in every chapter in the text and often in the illustrations. Attention has been called to the newly devised Electron Microscope with its greatly increased magnifying power and resolution over the ordinary microscope; to Polaroid for the micro-polariscope; to some new plastics for mounting in place of Canada balsam; to the high-pressure mercury lamps for ultraviolet radiation and the bright mercury lines for photographing objects with the microscope. In general, however, the book retains its former character." In addition to explaining the principles of the various forms of microscopes and how to use them, methods of preparing tissues, micro-drawing and photography and a brief history of lenses and microscopes included. Atmosphere is furnished by the author's dedication to the memory of his pupil Theobald Smith.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 26, No. 6, Philadelphia Number). November, 1942. Pp. 1935; many illustrations. Philadelphia: W. B. Saunders Company, 1942. Price, year, \$6.00.

THIS compact volume on endocrinology offers a very useful and practical approach to a subject which can be confusing and theoretical. Our present limitations in both diagnosis and therapy are well outlined, although in most cases future possibilities are suggested. The occasional instances of repetition and antagonistic opinions, necessitated by a work of this kind, in most cases, add to rather than detract from the value of the book. The only noteworthy omission is that of a section devoted to parathyroid disorders. All in all—a valuable summary of present-day endocrinology for both the specialist and the general medical practitioner.

W. K.

NEW BOOKS

Understand Your Ulcer. By BURRILL B. CROHN, M.D., F.A.C.P., Associate in Medicine, Gastro-Enterology, Mt. Sinai Hospital, New York; Associate in Medicine, Columbia University. Pp. 199; 19 figures, various tables. New York: Sheridan House, Publishers, 1943. Price, \$2.50.

Virus Diseases. By Members of the Rockefeller Institute for Medical Research; THOMAS M. RIVERS, M.D., WENDELL M. STANLEY, Ph.D., LOUIS O. KUNKEL, Ph.D., RICHARD E. SHOPE, M.D., FRANK L. HORSFALL, JR., M.D., and PEYTON ROUS, M.D. Pp. 170; several plates. Ithaca, N. Y.: Cornell University Press, 1943. Price, \$2.00.

Autonomic Regulations. By ERNST GELLHORN, M.D., Ph.D., Professor of Physiology, College of Medicine, University of Illinois. Pp. 373; 80 illustrations and frontispiece. New York: Interscience Publishers, Inc., 1942. Price, \$5.50.

Fundamentals of Immunology. By WILLIAM C. BOYD, Ph.D., Associate Professor of Biochemistry, Boston University, School of Medicine; Associate Member, Evans Memorial, Massachusetts Memorial Hospitals, Boston. P. 446; 45 illustrations. New York: Interscience Publishers, Inc., 1943. Price, \$5.50.

Orthopedic Subjects. Military Surgical Manual IV. Prepared and Edited by the Subcommittee on Orthopedic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council; GEORGE E. BENNETT, Chairman. Pp. 306; 79 figures. Philadelphia and London: W. B. Saunders Company, 1942. Price, \$3.00.

Manual of Oxygen Therapy Techniques Including Carbon Dioxide, Helium and Water Vapor. By ALBERT H. ANDREWS, JR., M.D., Director, Oxygen Therapy Department and Assistant Attending Otolaryngologist, St. Luke's Hospital, Chicago; Instructor in Laryngology, Rhinology and Otology (Broncho-esophagologist), Children's Memorial Hospital, Chicago; Former Research Instructor, Department of Physiology and Pharmacology, Northwestern University Medical School. Pp. 191; 32 figures, 16 tables. Chicago: The Year Book Publishers, Inc., 1943. Price, \$1.75.

The value of this book lies in the fact that it includes a fairly complete list of commercial apparatus with many of the directions for using. Besides this, it has some of tried improvisations for hospital usage. Its attitude toward methods and values is one of optimism to a degree which limits its scope as an accurate reference work; but its details and suggestions make the book useful in its field. C. C.

The Infectious Diseases of Domestic Animals, With Special Reference to Etiology, Diagnosis, and Biologic Therapy. By WILLIAM ARTHUR HAGAN, D.V.M., D.Sc., Professor of Bacteriology and Dean of the Faculty, New York State Veterinary College, Cornell University. Pp. 665; 145 figures. Ithaca, N. Y.: Comstock Publishing Company, Inc., 1943. Price, \$6.00.

Psychosomatic Medicine. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University Medical School, Philadelphia; and O. SPURGEON ENGLISH, M.D., Professor of Psychiatry, Temple University Medical School. Pp. 687. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$8.00.

Indigestion—Its Diagnosis and Management. By MARTIN E. REHFUSS, M.D., Professor of Clinical Medicine; and SUTHERLAND M. PREVOST, Lecturer in Therapeutics, Jefferson Medical College, Philadelphia. Pp. 556; 63 illustrations. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$7.00.

Food-Allergy. By ARTHUR F. COCA, M.D., Medical Director, Lederle Laboratories. Pp. 158; several tables. Springfield, Ill.: Charles C Thomas, 1943. Price, \$3.00.

Atlas of Ovarian Tumors. By GEMMA BARZILAI, M.D., New York City; Preface by FRED W. STEWART, M.D., Pathologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City. Pp. 264; 258 illustrations. New York: Grune & Stratton, 1943. Price, \$10.00.

Lymph Node Metastases. By GRANTLEY WALDER TAYLOR, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital; Surgeon, Collis P. Huntington Memorial Hospital and Pondville Hospital, Massachusetts Dept. of Public Health; and IRA THEODORE NATHANSON, M.S., M.D., Instructor in Surgery, Harvard Medical School; Assistant Surgeon, Collis P. Huntington Memorial Hospital; Beth Israel Hospital, and Pondville Hospital, Massachusetts Dept. of Public Health; Assistant in Surgery, Massachusetts General Hospital. With a Foreword by SHELDS WARREN, M.D., Assistant Professor of Pathology, Harvard Medical School, Boston. Pp. 498; 117 tables, 61 figures. New York: Oxford University Press, 1942. Price, \$8.00.

NEW EDITIONS

Outline of Psychiatric Case-Study. By PAUL WILLIAM PREU, M.D., Assistant Professor of Psychiatry and Mental Hygiene in the Yale University School of Medicine, Physician-in-Charge of the Psychiatric Clinic of the New Haven Hospital; Associate Psychiatrist to the New Haven Hospital. With Foreword by EGUEN KAHN, M.D. Second Edition. Pp. 279. New York: Paul B. Hoeber, Inc., 1943. Price, \$2.75.

The Anatomy of the Nervous System. By STEPHEN WALTER RANSON, M.D., PH.D., Formerly Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago. Seventh Edition. Pp. 520; 408 illustrations, some in color. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$6.50.

This edition has extensive revisions in the sections on the cerebellum, thalamus, hypothalamus, cerebral cortex and sympathetic nervous system. There are many new illustrations. The new parts on respiration and blood pressure (including the carotid body and carotid sinus), on the function and lesions of the hypothalamus, and on the optic pathways, are welcome additions. Some of the old material has been rearranged and simplified. Dr. Ranson, after completing this revision, has selected Dr. Sam L. Clark, a former student, as his successor for future editions. M. H.

Textbook of Biochemistry. By BENJAMIN HARROW, PH.D., Professor of Chemistry, City College of the City of New York. Third Edition. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$4.00.

The 3d edition of this well-known text in biochemistry is, like the former editions, rather concise with a minimum of the pro and con discussion of debatable subjects. It has been brought up to date in many respects, and in spite of the condensed manner in which it is written, the present edition contains about 100 pages more than the preceding edition. There are some omissions (*e. g.*, multiple alternate oxidation of fatty acid is not mentioned), which in the opinion of the Reviewer might well have been included even at the risk of making the book a little longer. J. J.

A Textbook of Clinical Neurology. By ISRAEL S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University, New York; Neurologist, The Mount Sinai Hospital; Consulting Neurologist, The Montefiore and Rockland State Hospitals, New York. Fifth edition. Pp. 840; 162 illustrations. Philadelphia & London: W. B. Saunders Company, 1943. Price, \$7.50.

The 5th edition of this well-established textbook on clinical neurology maintains the high standard of all of the previous editions. The additions have been carefully evaluated and presented in a concise manner. The brief references to electroencephalography and arteriography are adequate in their epitomized form. The sections on treatment become increasingly valuable with each new edition. Any review of this text, without again commending the author for the final chapter on the introduction to the history of neurology, would not be complete. S. H.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

G. LYMAN DUFF, M.A., M.D., PH.D.

STRATHCONA PROFESSOR OF PATHOLOGY, MCGILL UNIVERSITY

AND

E. G. D. MURRAY, O.B.E., M.A., L.M.S.S.A., F.R.S.C.

PROFESSOR OF BACTERIOLOGY AND IMMUNITY, MCGILL UNIVERSITY
MONTREAL, CANADA

PATHOLOGIC LESIONS FOLLOWING THE ADMINISTRATION OF SULFONAMIDE DRUGS

THE dramatic clinical results that followed the introduction of the sulfonamide drugs, their ease of oral administration and their relatively low toxicity, soon led to widespread use of these chemotherapeutic agents. However, as reports of clinical studies multiplied there appeared in the literature numerous instances of toxic reactions referable to these drugs. Most of these toxic manifestations were of a mild and relatively transitory nature and quickly subsided when administration of the drug was discontinued, but occasionally they were followed by death. The great majority of the early reports of the toxic effects of the sulfonamides were of a clinical character and rarely described pathologic lesions. With the more recent introduction of the newer sulfonamide compounds, toxicity studies on animals have been carried out, fatal clinical cases with autopsies have been reported and there has accumulated in the literature sufficient evidence to support the view that significant and recognizable pathologic lesions may follow the use of these drugs.

It is the object of this Review to describe those pathologic lesions, both in experimental animals and in man, that have been attributed to the various sulfonamide drugs. Whether these lesions are the result of individual idiosyncrasy or acquired sensitivity to the sulfonamides is beyond the scope of this paper. It is, however, obvious that toxic clinical manifestations, pathologic lesions and even deaths may occur following dosages of the drugs that are regarded as being within therapeutic limits. The various organs in which lesions have been described will be dealt with *seriatim* and the particular sulfonamide compound concerned in each instance will be mentioned in its appropriate place.

Heart. French²³ has produced a form of interstitial myocarditis in rats and mice by intraperitoneal injections of neoprontosil, sulfanila-

mide, sodium sulfapyridine or sodium sulfathiazole. This myocarditis is characterized by accumulations of mononuclear cells together with moderate numbers of eosinophils. Nelson⁶⁵ mentioned 1 hen in a series of experimental animals that showed an interstitial myocarditis following sulfanilamide treatment.

French and Weller²⁴ examined the hearts of 283 patients known to have received one or more of the sulfonamide drugs before death. After excluding cases in which only very small doses had been given shortly before death, cases in which myocardial changes were so slight as to be negligible and cases of disease with which interstitial myocarditis is known to be associated, these investigators were left with a group of 126 cases (44.5% of the original 283) in which significant interstitial myocarditis was present. The myocardial lesions were paravascular and interstitial in position and occurred in both auricles and ventricles and occasionally in the epicardium. The exudate consisted of large mononuclear cells, numerous cells with eosinophilic cytoplasm and many young neutrophils. Occasional foci of Zenker's hyaline necrosis were noted in the muscle fibers but no abscesses were present. A control series of cases failed to show such eosinophilic myocarditis. It is interesting to note that no examples of myocarditis were found among cases in which the use of the drugs had been discontinued more than 30 days prior to death. French and Weller²⁴ also mentioned that eosinophilic infiltrations were seen in the lungs, liver, kidneys, bone-marrow, spleen and lymph nodes of both human cases and experimental animals.

Rich^{77a} has recently reported 3 cases in which sulfonamide drugs and type specific sera for pneumonia and meningitis, respectively, were administered. In each of these cases an interstitial myocarditis with mononuclear cells, neutrophils and eosinophils was present. Although Clark and Kaplan⁸ have noted a similar type of myocarditis in serum sickness in the absence of the sulfonamides, and Apitz⁴ has produced like lesions in sensitized animals with foreign proteins, the possibility that hypersensitivity to the sulfonamides is the cause of the myocarditis cannot be dismissed. Schonholzer⁸⁷ and Davis¹⁵ have demonstrated that sulfonamides can attach themselves to plasma proteins and thus, perhaps, may act as specific antigens. Wedum⁹⁹ has succeeded in sensitizing guinea-pigs with sulfapyridine linked to human serum. Rich^{77a} suggested that the eosinophilic myocarditis observed by French and Weller,²⁴ and in 1 of his own cases^{77b} in which sulfathiazole alone was given, may have been the result of hypersensitivity to the sulfonamides. Duff¹⁸ has observed a case in which death from periarteritis nodosa followed a second course of treatment with sulfathiazole after a 30-day interval and in which at autopsy there was found a widespread eosinophilic interstitial myocarditis.

Lederer and Rosenblatt,⁵⁰ in their series of 4 cases of death due to sulfathiazole, reported 1 in which the left atrium of the heart showed several irregular areas of poorly preserved muscle fibers surrounded by partially broken-down neutrophils, small and large round cells and eosinophils. In other areas the myocardial fibers were swollen and the nuclei pyknotic or absent. Simon⁹⁰ also noted focal necrosis in the epicardium and a mild interstitial myocarditis in a patient who died after sulfathiazole therapy.

Blood-vessels. Lehr and Antopol⁵¹ reported that white mice given a single fatal intraperitoneal injection of sodium sulfadiazine and surviving 5 to 7 days showed a pronounced sclerosis of the arterial tree, especially the thoracic aorta. The inner surface of the aorta was white and wrinkled. Histologically, there was calcification and necrosis of the media. Antopol, Lehr, Churg and Sprinz² also noted pronounced calcification of the media of the arterial tree, especially in the aorta, following a single and repeated intraperitoneal injections of the sodium salts of sulfapyridine, sulfathiazole or sulfamethylthiazole in rats. Rich^{77a} has recently reported a series of 5 cases in which vascular lesions histologically indistinguishable from periarteritis nodosa were found in various organs and tissues of patients who had suffered from serum sickness following specific serum therapy and the administration of different sulfonamide compounds. In 2 additional cases^{77a,b} similar vascular lesions were found at autopsy following treatment with sulfathiazole alone. Duff¹⁸ has also recently observed a case of slightly atypical periarteritis nodosa involving the lungs, liver, spleen and kidneys in a previously healthy man who was admitted to hospital with a fracture of the tibia and fibula and who had received two courses of sulfathiazole therapy during his stay in hospital, the second course continuing up to the day of death. Rich^{77a,b} offered his observations as evidence in support of the idea that periarteritis nodosa may be a manifestation of hypersensitivity. He concluded that sensitization to the sulfonamides does occur and that under such circumstances vascular lesions as described above may be caused by the administration of sulfonamides.

Lungs. Merkel and Crawford⁶¹ reported 4 cases in which death had occurred after sulfathiazole therapy. At autopsy there was found in all lobes of the lungs small, gray foci of necrosis, pinhead to miliary in size. Microscopically, these foci of necrosis were surrounded by variable numbers of neutrophils. None of the foci of necrosis showed any reactive fibrosis and bacterial stains revealed no tubercle bacilli or other organisms. Lederer and Rosenblatt⁵⁰ described 4 patients who died after sulfathiazole therapy; in 1 of these, confluent areas of focal necrosis in the lungs were found at autopsy. These areas were made up of a central core of amorphous material in which there could be demonstrated fibrin and nuclear fragments. The necroses were surrounded by varying but small numbers of neutrophils and some small and large mononuclears. Stains for bacteria were negative. In 1 other of their 4 cases they found foci of necrosis in the trachea.

Liver. Although Domagk¹⁷ did not describe any pathologic changes in the livers of his experimental animals given Prontosil Insoluble, clinical experience soon showed that jaundice was one of the toxic manifestations of the sulfonamides. The changes produced experimentally in the liver have been variable in degree and type. Thus, Molitor and Robinson⁶³ in chronic toxicity experiments with sulfanilamide in rats stated that "except for some degenerative changes, the findings in the liver were not significant." Davis, Harris and Schmeisser¹⁶ injected sulfanilamide into the abdominal wall of white rats for 3 months and found only coarse granularity of the liver cells. In the experiments of Machiella and Higgins^{57a} foci of necrosis were observed in the livers of 30% of rats given varying doses of sulfanilamide for varying periods of time.

Similar lesions, however, were seen in 25% of the control animals. The livers of monkeys given sulfapyridine by mouth were described by Antopol and Robinson^{3b} as showing separation of the capillaries from the liver cell cords with granular material in the intervening spaces. They regarded these changes as being similar to the "serous hepatitis" of Rössle-Eppinger. Feinstone *et al.*²⁰ in a series of chronic toxicity experiments with sulfapyridine in monkeys, noted vacuolation of the liver cells and pigment in Kupffer cells but no necrosis. Rake, Van Dyke and Corwin⁷⁴ fed mice on a diet containing 2% sulfapyridine and found focal necrosis in the liver. Mice on similar diets containing 1% and 2% sulfathiazole showed similar lesions as well as cloudy swelling, fat infiltration and hyaline necrosis. Rats and monkeys, on the other hand, showed no liver lesions when fed on diets containing 0.5% to 1% sulfathiazole or sulfapyridine. Antopol, Lehr, Churg and Sprinz² noted that after single and repeated intraperitoneal injections of sulfathiazole, sodium sulfathiazole or sulfamethylthiazole in rats, severe degenerative changes appeared in the livers. Usually these liver changes occurred in association with concrements in the kidneys. Nelson⁶⁵ gave fatal doses of sulfanilamide to 21 hens, among which 17 showed a diffuse fatty change in the liver in contrast to control animals in which such alterations were absent. In most of the experimental animals the Kupffer cells contained abnormal amounts of hemosiderin pigment. One hen showed coagulation necrosis of the liver.

The liver lesions observed in human beings following deaths from the sulfonamides are also somewhat variable in type but for the most part are characterized by extensive focal necrosis. Cline¹⁰ reported the case of an 18 year old youth who died following treatment with sulfanilamide for gonorrhea. At autopsy the liver was found to be reduced in size, weighing 1200 gm. Microscopically, there was dissociation of the liver cell cords and massive destruction of liver cells. The remaining liver cells showed a "fatty change." No inflammatory exudate was present and the picture resembled acute yellow atrophy. Russel⁸² reported a patient who took 1250 gr. (80 gm.) of sulfanilamide over a 6-week period. Ten days later the patient became jaundiced. At autopsy the liver was found to be markedly reduced in size, weighing 600 gm. The capsule was wrinkled and the organ was flabby. Microscopically, there was extensive necrosis of the liver cells.

Ginzler and Chesner²⁶ reported a case of acute yellow atrophy of the liver associated with necrosis in other organs in a newborn infant following administration of sulfanilamide to the mother. These authors suggested that sulfonamides may produce toxic effects in the fetus by passage through the placenta. Focal necrosis with degenerative changes in liver cells was described by Tragerman and Goto⁹⁶ in a patient with gonorrhea dying after sulfanilamide treatment. Berger and Applebaum⁵ cited a case in which the patient took 6.6 gm. of sulfanilamide over a 3-day period. Two weeks later he took an additional 20 gm. within a period of 10 days and died 1 month later with progressive jaundice. At autopsy, the liver was small, firm and finely granular. Microscopically, the liver cells showed degenerative changes and foci of necrosis were encountered. In a general review on the sulfonamides, Greene and Hotz²⁸ mentioned a case in which jaundice suddenly appeared during treatment with sulfanilamide for hemolytic streptococci.

septicemia. At autopsy, areas of portal focal degeneration with leukocytic infiltration were found in the liver.

Liver lesions in fatal cases of hemolytic anemia following ingestion of sulfapyridine have been noted. Ravid and Chesner⁷⁶ reported a case of fatal hemolytic anemia following the ingestion of 8 gm. of sulfapyridine. At autopsy the liver showed patchy cytoplasmic vacuolation with a tendency toward central localization and the Kupffer cells were found to be loaded with hemosiderin. In an investigation of the acute hemolytic anemias caused by the sulfonamides, Fox and Ottenberg²² described 1 fatal case treated with sulfapyridine in which foci of necrosis were found in the liver at autopsy.

The most extensive and widespread focal necrosis of the liver has been reported in deaths following sulfathiazole therapy. Lederer and Rosenblatt⁵⁰ in their series of 4 cases, Merkel and Crawford⁶¹ in an additional 4 cases and Simon⁹⁰ in his single case, observed identical, widespread, extensive focal necrosis of the liver of coagulation type. These foci of necrosis were found in all portions of the hepatic lobules and were occasionally surrounded by a sparse infiltration of neutrophils. Stains for bacteria in all instances were negative.

Bone-marrow and Blood. The hemolytic anemias encountered during sulfonamide therapy fortunately improve after discontinuance of the drug. It appears that the hemolysis is probably peripheral, but certain changes have been described in the bone-marrow as well as in the red blood cells themselves. Hageman³⁵ reported an increase in the eosinophils in the bone-marrow of mice injected with sulfanilamide. Kreutzman and Carr⁴⁹ also reported an increase of the eosinophils in the marrow of rabbits given Prontosil. This they regarded as evidence of early bone-marrow depression. Similar eosinophilic infiltrations of bone-marrow were observed by French and Weller²⁴ in their human material after sulfonamide therapy. Richardson,⁷⁸ on the contrary, found no eosinophilia or other changes in the bone-marrow of mice made anemic with sulfanilamide; and Osgood,⁶⁷ working on marrow cultures infected with streptococci, stated that sulfanilamide did not appear to have a direct toxic action on the nucleated cells. Machella and Higgins^{57b,c} and Higgins and Machella⁴⁰ produced anemia in rats with sulfanilamide. They found that the bone-marrow showed a reticulocytosis, macrocytosis and anisocytosis and that there was a slight increase in the transverse diameter of the red blood cells. They noted that the myeloid stimulation after 4 days of sulfanilamide was greater than the erythroid, but after 6 days (when the anemia was marked) the erythroid stimulation was greater than the myeloid. This reversal of activity is probably a response to increased blood destruction.

Paul and Limarzi⁶⁹ found, in human beings receiving therapeutic doses of sulfanilamide, that the sternal bone-marrow showed a normoblastic reaction. Koletsky⁴⁶ reported a fatal case of hemolytic anemia in which, at autopsy, erythropoietic hyperplasia of the bone-marrow was noted. Ravid and Chesner⁷⁶ have also reported moderate hyperplasia of the erythropoietic elements in the bone-marrow in a fatal case of hemolytic anemia following 8 gm. of sulfapyridine.

Actual pathologic lesions within the red blood cells have been reported by Moeschlin.⁶² He described so-called "inner bodies," which were found at the margins of the red blood cells at the height of the clinical

cyanosis. These bodies can only be stained supravitaly with brilliant cresyl blue. They are found in the reticulocytes of the bone-marrow in small numbers but only after they have appeared in the peripheral blood and only after a mild degree of anemia has been produced. Richardson,⁷⁸ studying anemia in mice produced by sulfanilamide, noticed the presence of the so-called "Heinz bodies" in the red blood cells. Similar bodies have been described by Ehrlich and Lazarus¹⁹ in a variety of anemias produced by agents that also cause formation of abnormal pigments.

The pathologic lesion associated with agranulocytosis produced by the sulfonamides is fairly well established and consists primarily of an arrest of maturation of the cells of the granular series in the bone-marrow with destruction of the more adult forms. Experimentally, this was noted in 1 rat by Davis, Harris and Schmeisser¹⁶ following sulfanilamide injections. The bone-marrow showed an arrest of maturation of the myeloid cells with complete absence of granulocytes.

Clinical cases of fatal agranulocytosis following sulfonamide therapy have shown changes in the bone-marrow varying from aplasia to mild depression of the granular series. Young¹⁰¹ reported a case of agranulocytosis following sulfanilamide in which the bone-marrow was aplastic and contained no granulocytes. Schwartz, Garvin and Koletsky⁸⁸ in their case of agranulocytosis following sulfanilamide, stated that the distinctive feature of the bone-marrow was the complete absence of granulocytes and even of myelocytes with reversion of the myeloid series to a stem cell type. Garvin,²⁵ Schecket and Price,⁸⁶ Pearson,⁷¹ Rinkoff and Spring,⁷⁹ Tragerman and Goto,⁹⁶ and Robb⁸⁰ reported essentially the same findings in the bone-marrow in their fatal cases of agranulocytosis following sulfanilamide. Kennedy and Finland⁴⁵ reported a fatal case of agranulocytosis following both sulfapyridine and sulfathiazole therapy. The autopsy findings in the bone-marrow were similar to those described above.

Greenwald, Litwins and Spielholz²⁹ reported an interesting case of polycythemia vera in which anemia and leukopenia followed sulfanilamide therapy. At the height of the white cell depression a sternal biopsy showed a complete arrest of maturation at the metamyelocyte level. Six months later, after recovery, another sternal puncture revealed a return to active formation of mature white blood cells. That sulfanilamide may have a direct toxic effect on white blood cells has been demonstrated by Coman¹¹ who, in his experiments on chemotropism, showed that leukocytes lose their ameboid motions in dilute solutions of sulfanilamide.

Lederer and Rosenblatt⁵⁰ and Merkel and Crawford⁶¹ found foci of necrosis in the bone-marrow in 5 of their 8 cases (4 each) of death following sulfathiazole therapy. This was part of a general necrotizing process seen in other organs. They did not notice any arrest of maturation of the granular series.

Spleen. The majority of reports dealing with splenic lesions concern observations on animals during the course of toxicity experiments. The splenic changes in animals are of a mild and variable nature and apparently not all species react alike, even to similar doses of the same drug. It also appears that many of the changes seen in the spleens of

experimental animals are secondary to the anemias produced during the experiments.

Hageman,³⁵ injecting Swiss mice with sulfanilamide, found that the spleens of these animals showed varying amounts of hemosiderin adjacent to the Malpighian bodies. Similar results were obtained by Antopol and Robinson³⁶ in rats, rabbits and monkeys with sulfapyridine. Wien¹⁰⁰ noted that rats given sulfanilamide showed dilatation of the sinusoids and hemosiderin deposits which he interpreted as indicative of an exaggeration of the hemolytic process accompanying the anemia. The spleens of the rats given sulfapyridine showed no abnormalities. Richardson⁷⁸ also found that in anemias in mice produced by sulfanilamide, the spleens were enlarged and showed an increase in iron pigment. Molitor and Robinson⁶³ in chronic toxicity experiments with sulfanilamide carried out on rats, rabbits and dogs found, in rats only, enlargement of the spleens which were engorged with blood and contained both iron- and non-iron-bearing pigments.

Rake, Van Dyke and Corwin,⁷⁴ and Rake, Van Dyke, Corwin, McKee and Greep⁷⁵ noted that mice fed on diets containing 0.5 % to 1 % sulfapyridine showed no lesions in their spleens, whereas mice fed on 1 % sulfathiazole showed dark red, small spleens in which the Malpighian bodies were small, appeared disorganized and contained pyknotic cells. The spleens of mice on a 2 % sulfathiazole diet showed disorganization of germinal centers and pyknosis of the lymphoblastic cells with their ultimate disappearance. No splenic lesions were noted in rats or monkeys given either sulfapyridine or sulfathiazole. Davis, Harris and Schmeisser¹⁶ injected white rats with sulfanilamide over a 3-month period. The spleens of their animals revealed hyperplasia of the reticular cells. In several animals focal areas of necrosis were seen in the Malpighian bodies. The spleens also showed increased iron-containing pigment. Corwin¹³ in his chronic toxicity experiments with sulfaguanidine in rabbits noted a reduction in the size of the spleen with atrophy of the Malpighian bodies and pulp. Similar lesions could not be found in the spleens of dogs or monkeys treated with sulfaguanidine. Climenko and Wright⁹ produced with sulfathiazole and sulfapyridine a "toxic splenitis with slight erythrophagocytosis" in monkeys.

In man, both Lederer and Rosenblatt⁵⁰ and Merkel and Crawford⁶¹ reported extensive focal necrosis in the spleens of patients dying after sulfathiazole therapy. While the majority of the foci were in or near the peripheral parts of the Malpighian bodies, occasional foci of necrosis were seen in other parts of the spleen. Simon⁹⁰ also reported occasional foci of necrosis in the spleen in his case of death following sulfathiazole therapy. Lederer and Rosenblatt⁵⁰ also described an associated hyperplastic change in the reticulum.

Lymph Nodes. As part of the general necrotizing process observed in their 4 cases of death following sulfathiazole, Merkel and Crawford⁶¹ found in all instances enlarged, boggy lymph nodes at autopsy. Lederer and Rosenblatt⁵⁰ found only 1 case (in their series of 4) in which the lymph nodes showed similar lesions. These lesions consisted of foci of coagulation necrosis without infiltration by neutrophils. No bacteria were present. Only Molitor and Robinson⁶³ have reported changes in the lymph nodes of experimental animals; these lesions do not appear to have been very marked or specific.

Adrenals. Antopol and Robinson^{3b} noted enlargement of the adrenal glands in rats with widening of the fascicular layer when these animals were treated with sulfapyridine. In their experiments with sulfathiazole, sulfamethylthiazole and sodium sulfathiazole, Antopol, Lehr, Churg and Sprinz² again noted enlargement of the adrenal glands and in these experiments observed that the zona fasciculata took a deep eosinophilic stain and that occasional foci of necrosis were present in the medulla. In contrast to these experimental findings, Merkel and Crawford,⁶¹ Lederer and Rosenblatt⁵⁰ and Simon⁹⁰ found foci of necrosis in the cortex without medullary lesions in their cases of death following sulfathiazole therapy.

Kidneys. As early as 1937, Oakley⁶⁶ observed concretions in the renal tubules of mice following single or repeated small doses of Prontosil. He noted that the kidneys were enlarged and that the straight and convoluted tubules were dilated. He believed that death was due to renal obstruction. In 1938 Kolmer, Brown and Rule⁴⁸ gave sulfanilamide to rabbits and noted only mild cloudy swelling of the renal epithelium which they did not regard as significant. These investigators reported no concretions in the kidney tubules. Davis, Harris and Schmeisser¹⁶ also observed no concretions in the renal tubules of rats injected with sulfanilamide but mentioned cloudy swelling and mild increase of fat in the tubular epithelium. Molitor and Robinson⁶³ in their chronic toxicity experiments in rats with sulfanilamide observed collections of brown, granular pigment in the convoluted tubules of the kidneys. Only a small amount of this pigment stained positively for iron. Nelson⁶⁵ gave fatal doses of sulfanilamide and sulfanilyl sulfanilamide to rabbits and observed epithelial degeneration, casts and debris in the renal tubules with dilatation of the tubules. In hens treated with sulfanilamide, he noted considerable fatty changes in the epithelium of the kidney tubules.

In 1939, however, with the introduction of sulfapyridine, Antopol and Robinson,^{3a} using rats, rabbits and monkeys, and Gross, Cooper and Lewis,³¹ using rats, reported independently and simultaneously the formation of uroliths in their experimental animals in the course of toxicity studies on sulfapyridine. These investigators noted that the kidneys were enlarged and dilated and that pelvis and ureters were also dilated. They found yellow or white, spiculated concretions in calyces, pelvis, ureters and bladder and believed that the pyelonephritis, pyelitis, ureteritis, hydronephrosis and hydroureters observed were secondary to the uroliths. These uroliths were found to be composed of relatively insoluble acetyl derivatives of sulfapyridine. Marshall and Litchfield⁵⁹ showed that when the sodium salt of acetyl sulfapyridine is injected intravenously into animals, concretions form in the renal tubules. Toomey⁹⁴ working with monkeys noted the appearance of uroliths following sulfapyridine and thus corroborated the findings mentioned above. Antopol and Robinson^{3b} repeated their work on rats, rabbits and monkeys with sulfapyridine and found uroliths and associated changes. Toomey, Reichle and Takacs⁹⁵ gave monkeys doses of sulfapyridine slightly less than that recommended for infants of comparable weight and found concretions in the renal tubules, pelvis, ureters and bladder with resulting inflammation and slight necrosis. Although this inflammation was thought to be due to obstruction of renal outflow

by crystals with subsequent infection, these authors felt that an immediate toxic effect of the drug on the epithelium of the convoluted tubules could not be excluded.

In testing the toxicity of sulfathiazole and sulfapyridine in monkeys, Van Dyke, Greep, Rake and McKee⁹⁷ found that only 1 monkey out of 7 died in uremia due to urinary obstruction following sulfathiazole whereas 6 out of 7 monkeys on sulfapyridine showed bilateral hydro-ureters and hydronephrosis. Climenko and Wright⁹ also produced urolithiasis and degenerative changes in the renal epithelium of monkeys with sulfathiazole and sulfapyridine. While monkeys and rats show more extensive urolith formation with sulfapyridine than with sulfathiazole this apparently does not hold true for mice as demonstrated by Rake, Van Dyke and Corwin.⁷⁴ Gross, Cooper and Scott,³³ who coined the term "urolithiasis medicamentosa" for the uroliths caused by the sulfonamides, also noted that, in rats, concretions in renal tubules were three times as frequent with sulfathiazole as with sulfamethylthiazole whereas stones in the renal pelves, ureters and bladder were twice as common with sulfamethylthiazole as with sulfathiazole. Antopol, Lehr, Churg and Sprinz² gave single and repeated intraperitoneal injections of sulfathiazole and sodium sulfathiazole to rats and noted that sulfathiazole produced a calcifying nephrosis of the collecting tubules. Similar calcific deposits were noted in the cortex. They also, like Gross, Cooper and Scott,³³ noted that concretions in the renal tubules were more frequent with sulfathiazole whereas extrarenal concretions were more common with sulfamethylthiazole.

Other sulfonamide compounds have also been found to produce uroliths in experimental animals. Feinstone *et al.*²⁰ produced uroliths in kidneys and bladders of monkeys with sulfadiazine. The kidneys showed some evidence of damage as indicated by regeneration of the tubular epithelium. Lehr and Antopol⁵¹ gave single fatal intraperitoneal injections of sodium sulfadiazine to white rats and in addition to the uroliths noted calcification of the distal convoluted tubules, Henle's loops and collecting tubules. Animals surviving repeated injections showed severe histologic damage to the renal epithelium. Gross, Cooper and Hagan³⁰ reported urolithiasis medicamentosa following sulfadiazine in mice and pointed out that the sulfadiazine crystals are not sharply spiculated and, therefore, are not likely to cause hematuria. Corwin¹³ in chronic toxicity experiments with sulfaguanidine in rabbits found crystals in the renal tubules, pelves, ureters and bladder. Dogs showed only a few lesions resembling healed pyelonephritis, while no kidney lesions or stones were found with this drug in monkeys.

It is interesting to note that no distinctive glomerular lesions have been reported in experimental animals following the sulfonamides. The glomerular lesions described by Gross, Cooper and Morningstar³² are inconclusive, as these authors readily admit.

In human beings dying from renal obstruction following the sulfonamides, the search for uroliths both grossly and microscopically is often fruitless. Antopol¹ described the findings in a patient dying with renal complications after sulfapyridine; he was unable to demonstrate uroliths either grossly or microscopically. He stated that the findings in the kidneys were reminiscent of the non-specific, degenerative changes encountered in experimental animals following sulfapyridine therapy.

He suggested that the uroliths may dissolve or wash out in microscopic preparation. Koletsky and King⁴⁷ reported a case of fatal renal insufficiency following 8 gm. of sulfapyridine. At autopsy, there was found severe, necrotizing, suppurative and hemorrhagic ureteritis and pyelitis without any crystals being found grossly or microscopically. Stryker⁹¹ reported finding yellowish-white gravel in the calyces, pelvis and urinary bladder of a child following sulfapyridine therapy with microscopic deposits in the renal tubules. Pepper and Horack⁷² described crystalline deposits of sulfathiazole in the renal tubules in a patient dying in anuria after sulfathiazole. Sadusk, Waters and Wilson⁸⁴ reported a case of anuria following sulfapyridine therapy in which extensive necrosis of the renal pelvic wall was noted following obstruction of the ureter. Katzenstein and Winternitz⁴⁴ pointed out that rupture of the renal pelvis may follow sulfapyridine therapy. Hanson³⁶ was also able to demonstrate sulfapyridine crystals in the sediment which blocked the ureters in his case. He suggested that the renal parenchymal damage precedes the precipitation of the drug from solution.

That primary parenchymal damage to renal epithelium, regardless of urolith formation and obstruction, probably does occur is strongly suggested by the findings of Lederer and Rosenblatt,⁵⁰ Merkel and Crawford,⁶¹ and Simon,⁹⁰ who, although finding only a few peculiar bluish-red crystals in the tubules, noted extensive focal necrosis of renal epithelium. This necrosis was entirely out of proportion to the dilatation seen and the number of crystals observed. Occasionally the renal tubules may be plugged with hemoglobin, as in a fatal case of hemolytic anemia following sulfapyridine as reported by Ravid and Chesner.⁷⁸

Testicle. The widespread use of the sulfonamides in gonorrhea has raised the question whether spermatogenesis may be affected. Jaubert and Motz⁴³ and Marion *et al.*⁵³ examined the semen of patients being treated with various sulfonamides and reported a decrease in the number, vitality and motility of spermatozoa. This could not be confirmed by Heckel and Hori³⁹ with Prontylin. Shettles⁸⁹ mixed human semen, *in vitro*, with sulfanilamide or sulfapyridine in concentrations higher than those found in the body and observed no effect on the survival or activity of spermatozoa. Although Nelson⁶⁵ reported marked testicular damage with reduction in numbers of spermatozoa, necrosis of spermatids and spermatocytes in rabbits given sulfanilamide or sulfanilyl sulfanilamide, these findings could not be confirmed by Levaditi and Vaisman,⁵³ Pallizolli *et al.*,⁶⁸ Pautrier *et al.*,⁷⁰ or Cordonnier¹² in rabbits, guinea-pigs or mice.

Nervous System. Clinical symptoms suggesting peripheral neuritis and symptoms referable to the central nervous system following sulfonamide medication have been reported in the literature but pathologic lesions in human beings or experimental animals have been described but rarely. Custer *et al.*¹⁴ fed normal dogs 0.67 gm. of sulfanilamide per kg. and noted toxic reactions referable to the central nervous system. At autopsy, the brains appeared swollen, soft and edematous. Histologically, the edema was most marked along the periphery of the vessels. Ganglion cells showed degenerative changes varying from slight degrees of damage to complete cytolysis, most marked in the hippocampus, basal ganglia and cerebellum. In 1 instance there was ischemic necrosis in the lenticular nucleus. In the spinal cord and in the periph-

eral nerves, swelling of the myelin sheaths was noted in all animals, partial to complete demyelination occurring in some of the motor tracts. The anterior horn cells showed the same degenerative changes as the ganglionic cells of the brain. In 1 instance the sciatic nerve showed patchy replacement with strands of Schwann cells. The authors believed that these changes were due to edema and anoxia occurring as a result of injury to the capillary endothelium by sulfanilamide.

Hawking,³⁸ after large intraperitoneal injections of sulfanilamide to rabbits and cats, noted the development of decerebrate rigidity. At autopsy he found degenerative changes in the central nervous system, *e. g.*, chromatolysis in the neurones of the anterior columns of the spinal cord and in some of the nerve cells of the cortex and mid-brain. Feinstein *et al.*²⁰ observed in 2 out of 6 monkeys treated with sulfapyridine, swollen nerve fibers in the spinal cord with lymphocytic infiltration.

The nervous system of chickens, in particular, appears to be susceptible to damage by the sulfonamides. Bieter *et al.*⁶ gave oral doses of sulfanilamide, sulfapyridine, sulfathiazole, sulfanilyl dimethyl-sulfanilamide or sulfaphenylthiazole to chickens. All these drugs produced injury to the nervous system, the degree of severity ascending in the order given above. Sulfanilamide, the least toxic, produced condensation of the myelin of the peripheral nerves and mild swelling of the axons while the other drugs produced damage to the brain, spinal cord and peripheral nerves. In the latter the changes varied from condensation of the myelin to the formation of truncated cones, vacuolation and fragmentation of both myelin and axons. The spinal cord showed extensive damage with demyelination, vacuolation and shrinkage and pyknosis of nerve cells. The brains showed pyknosis and fragmentation of nerve cells, glial nodules and proliferation of the endothelium of the cerebral vessels which in some instances progressed to complete occlusion. Nelson⁶⁵ produced milder but essentially similar lesions in the sciatic nerves of hens by giving fatal doses of sulfanilamide. Rabbits showed similar lesions, though less frequently, following fatal doses of sulfanilamide and sulfanilyl sulfanilamide.

Reports of neuropathologic lesions attributed to the sulfonamides in human beings have been few. Fisher and Gilmour²¹ reported 2 cases of "encephalomyelitis" following the use of sulfanilamide. In 1 of these cases, in which an autopsy was performed, the pathologic lesions consisted of softening of the cord substance and various vascular lesions with hemorrhage and thrombosis in the small arteries and veins. The softening was accompanied by ballooning of the myelin sheaths and proliferation of the microglial cells. The authors admitted that this softening may have been due to vascular occlusion but believed the vascular occlusion was due to the toxic action of the sulfanilamide. Santo⁸⁵ reported a case of extensive demyelination, focal necrosis, gliosis and vacuolation of the spinal cord in a young man who had received 60 gm. of uliron (dimethyl derivative of sulfanilyl sulfanilamide). Roseman and Aring⁸¹ described the case of a young negro who had received sulfamethylthiazole. At autopsy there was found a hemorrhagic encephalopathy confined to the gray matter of the cerebral cortex and basal ganglia. The lesions consisted of perivascular hemorrhages and focal areas of necrosis and each occurred about a central capillary or precapillary vessel with either hyperplastic or necrotic

endothelium. In some of the vessels, thrombi were present. The neuronal damage was believed to be secondary to the vascular changes; the "indications are that the precipitating factor of the sulfamethylthiazole encephalopathy may be a toxic reaction on the vascular bed of the central nervous system."

The findings of Custer *et al.*,¹⁴ Fisher and Gilmour²¹ and Roseman and Aring⁸¹ all point to a toxic action of the sulfonamides upon the endothelium of the smaller vessels of the brain; the secondary changes in nerve tissue probably result from the edema and anoxia thus produced.

The local application of soluseptasine, solid sulfapyridine or solid sulfanilamide to the brains of rabbits does not, according to Russel and Falconer,⁸³ produce any damage to the brain tissue. They mentioned, however, that excess of these substances, due to low solubility, excites a foreign body reaction. Essentially similar observations were made by Hurteau⁴¹ who used sulfanilamide, sulfathiazole, sulfadiazine and sulfapyridine in cats. These findings are at variance with those of Pilcher, Angelucci and Meacham⁷³ who implanted sulfanilamide, sulfathiazole and sulfadiazine on the brain surface of normal dogs, all of which developed typical attacks of Jacksonian epilepsy. None of the control animals with like quantities of kaolin implanted on the brain developed epilepsy. Watt and Alexander⁹⁵ reported convulsions in cats when sulfathiazole was implanted intradurally but not with sulfanilamide, sulfapyridine, sulfadiazine or sulfacetamide. These authors also reported convulsions in 5 patients in whom sulfathiazole had been placed in craniocerebral wounds.

Skin. Skin rashes of various types following sulfonamide medication are well known but remarkably few histologic studies of these lesions have been made. Tedder⁹² made a microscopic study of the skin in 6 cases of sulfanilamide rash. The histologic pictures of the different types of eruption presented various stages of inflammation and could not be differentiated from sensitization dermatitis. An interesting picture was presented by a dermatitis precipitated by exposure to sunlight following sulfanilamide therapy. The pathologic changes were similar to those of arsenical dermatitis or acute lupus erythematosus. Loveman and Simon⁸⁶ noticed skin eruptions suggesting erythema nodosum following treatment with sulfanilamide. These lesions disappeared after a few days but could be made to reappear by giving the patient further sulfanilamide. A biopsy taken from one of these lesions showed a histologic picture that was indistinguishable objectively from that of erythema nodosum. A few Gram-negative diptheroids were present but these were not regarded as the etiologic agents.

Wounds and Serous Cavities. The present practice of combating infections in wounds and serous cavities by sprinkling them with the various sulfonamide powders raises the question of possible deleterious effects of the powders themselves. The work on this problem has been largely experimental.

Mellon and McKinney⁶⁰ studied the effects of sulfonamide compounds on the fibroblasts of chick embryo heart tissue cultures. These authors found that sulfanilamide induced an early inhibition of growth of the fibroblasts which were converted to macrophage type. The tissue, therefore, became syncytial instead of radiating uniformly from the explant. Glynn²⁷ made standard cutaneous incisions in rabbits, placed

powdered sulfanilamide, sulfathiazole or sulfapyridine in the wounds and observed them, 5, 7 and 14 days later. He noted a slight but barely significant inhibition of fibroblast proliferation by sulfathiazole and sulfapyridine but not by sulfanilamide. He found that sulfanilamide and to a lesser extent sulfapyridine had a slight but definite necrotizing action on muscle. This toxic effect on muscle has also been observed by Nelson.⁶⁵ Glynn,²⁷ however, did not believe that the slight inhibition of fibroblastic proliferation or toxic reaction are contraindications to the use of these drugs in wounds.

Bricker and Graham⁷ attempted to show by measurements of tensile strength of wounds that sulfanilamide given by mouth inhibits the healing of wounds in dogs. The observations of Mueller and Thompson,⁶⁴ Jackson and Coller⁴² and Harbison and Key³⁷ on the healing of wounds dusted with sulfanilamide powder indicated that no interference with healing or tensile strength of wounds occurs. Mueller and Thompson⁶⁴ found that infected wounds sprinkled with sulfanilamide powder healed with greater rapidity than did similar wounds not treated with the drug.

In serous cavities, the various sulfonamides act as mild irritants and may elicit a foreign body reaction. Hageman³⁵ injected mice intraperitoneally with sulfanilamide and noted a foreign body reaction. Throckmorton⁹³ placed powdered sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine, sulfamethyldiazine or sulfanilylguanidine into the peritoneal cavities of rats after surgical laparotomy and studied the cellular responses and local conditions. The cellular responses elicited by the sulfonamide compounds were, qualitatively, those of non-specific irritation. Their quantitative differences seemed to be related to factors of solubility and irritation. The most irritating was sulfapyridine. When clumps of the various drugs were rapidly walled off by viscera and omentum, such clumps were found surrounded by foreign body giant cells 14 days later. Organizing adhesions were frequent but only 1 case of partial intestinal obstruction was noted. Marked peritoneal irritation with the presence of blood-tinged fluid in the abdominal cavity was noted by Lehr, Antopol, Churg and Sprinz⁵² following injections of sulfapyridine or sulfamethylthiazole into the abdominal cavities of rats. Sulfathiazole caused less irritation though large amounts of clear fluid were usually found in both pleural and peritoneal cavities.

Tumor Formation. Hacren³⁴ injected 20 Swiss mice with sulfanilamide subcutaneously. Two mice developed a spindle cell sarcoma at the site of injection. This finding could not be substantiated by Zamecnik and Koletsky¹⁰² who gave repeated subcutaneous injections of sulfanilamide and of Prontosil suspended in oil, for 1 year. Lewis⁵⁴ injected sulfanilamide in olive oil subcutaneously in mice and failed to produce tumors. Moreover, he found that sulfanilamide injections did not cause mice to become refractory to implanted tumors nor did sulfanilamide injections cause regression of established tumors.

Summary. In this Review an attempt has been made to indicate and describe the various pathologic lesions that have been attributed to the sulfonamide drugs both in experimental animals and in man. In the heart, the lesions take the form of an interstitial myocarditis with occasional foci of necrosis. Blood-vessels, in man, may show

inflammatory lesions indistinguishable from those of periarteritis nodosa in the viscera; in the brain there appears to be injury to the vascular endothelium with associated secondary parenchymal damage. The liver lesions are characterized by widespread focal necrosis and, as part of a general necrotizing process, focal necroses may be found in the lungs, lymph nodes, spleen and adrenal glands. The kidneys and urinary tract may be damaged by urolith formation with obstruction and subsequent inflammation. In association with agranulocytosis, the bone-marrow shows an arrest of maturation of the granular series with destruction of the more adult forms; in cases of hemolytic anemia there is erythropoietic stimulation. The skin changes are of a non-specific inflammatory nature. The sulfonamides act as mild irritants and foreign bodies when placed in serous cavities. There is no valid evidence to indicate that the sulfonamides are capable of producing tumors. Inasmuch as the lesions that have been attributed to the sulfonamides in human beings have, for the most part, been reproduced in healthy experimental animals, it seems reasonable to conclude that the lesions described in human beings are due to the drugs employed rather than to the diseases for which the patients were being treated.

It is not the intention to overemphasize the dangers of these extremely valuable drugs, as Long, Haviland, Edwards and Bliss⁵⁵ fear. By bringing such lesions to general notice it is our purpose to point out the anatomic bases for clinically observed toxic reactions and to emphasize the physician's responsibility to exercise due care and caution in administering what may be, in certain individuals, a potentially dangerous, as well as extremely valuable drug.

MORRIS A. SIMON, M.D.

Director of Laboratories, Jewish
General Hospital, Montreal, Can.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.*

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

THE INFECTIOUS PERIOD OF POLIOMYELITIS AND VIRUS DETECTION†

Two clinically silent features of disease, the incubation and infectious periods, are as useful for epidemiologic purposes as the clinically manifest signs. Precise information concerning both is necessary for the establishment of case-to-case relationships, and may be of prime importance in laying down appropriate control measures.

Time and space relationships in the distribution of cases serve, to a considerable extent, as a guide in determining mechanisms of dissemination. An outbreak following the importation of a single case into an isolated and previously uninfected population group, a situation not often presented to the epidemiologist, affords an ideal opportunity for studying the relation between cases. Russell²⁷ has called Carter's¹¹ study of the extrinsic incubation period in yellow fever in such a situation, "as good an example of intelligent field epidemiology as can be found anywhere." The existence of an interval of time between primary and secondary cases had been noted that was longer than the usual incubation period of the disease. The phenomenon, however, had never been critically examined, for yellow fever was characteristically an urban disease where "the difficulties in tracing individuals and their contacts are almost insurmountable." Carter found an opportunity to pursue his inquiry "of the space of time which intervenes between the development of the first case which infected the environment and the development of cases contracted from this environment" in 1898 in Orwood, Miss.—"not a town or even a hamlet" but an agricultural neighborhood with farms seldom closer than a mile apart and having

* On active service in the armed forces of the United States.

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little intercourse with the outside world, and "practically all non-immune to yellow fever." He added two prerequisites for epidemiology and an epidemiologist—"people who were at once intelligent enough to know and honest enough to tell the truth and to coöperate in good faith with the efforts made to trace the infection of each case" and "Dr. Gant, who made the diagnosis of yellow fever, and under whom (directly or indirectly) all sanitary measures were conducted, was much beloved in the community, and had their entire confidence."

From detailed studies of the time sequence of cases and of exposures to infected households Carter found that upon introduction of a primary case the environment did not become infective until 2 to 3 weeks had elapsed, but was then infective even though the initial case was no longer present. Since the intrinsic incubation period was already well known to be not over 5 or 6 days, this extra period was called the "extrinsic incubation."

To Reed, influenced more by Carter's study than anything else in planning the experiment that was to make history, the extrinsic incubation period indicated a secondary host which did not travel far from the immediate abode of the primary case. For how could the infection always lie dormant for 2 weeks in fomites, then in the air as the favorite theory and as the basis of all attempts at prevention? From the vantage point of present knowledge—simple logic. But remember, all this took place only a few years after Theobald Smith had tapped the reservoir of insect transmission with ticks and Texas cattle fever; and just on the heels of Ronald Ross with *Anopheles* and malaria. Thus, with Carter's extrinsic incubation period Reed succeeded where, without it, Finley had failed to establish his long-held mosquito hypothesis either on epidemiologic grounds, or by experimental transmission.

Since the dissemination of the virus of poliomyelitis is accomplished for the most part through individuals who present no recognizable symptoms; it is usually not possible to determine whether a given case represents the introduction of the infectious agent, nor is it easy to group cases which are related one to the other in the epidemiologic sense. Similarly, it is exceptional when the infectious period can be determined from history of exposure to a previous case, or the incubation period measured from the interval between exposure and the onset of symptoms. Where contact between cases is seen as, for example, in multiple cases in families, exposure between the individuals has usually been continuous, so that the precise time of infection cannot be fixed. In 1929, Aycock and Luther⁷ collected data in instances of the disease following known exposure where some limit could be set on the time of exposure and on the interval between exposure and onset of the disease. The data comprised milk-borne outbreaks, cases following tonsillectomy, isolated small groups of cases in the same locality, and certain instances of multiple cases in families. Analysis of these sets of data, each of which served to set some limit on the time at which infection took place or on the interval between infection and onset of the disease, when taken together indicated an infective period extending from the 5th day preceding the onset of symptoms to the 5th day of the disease. From these data, it could likewise be ascertained that the incubation period was not necessarily under 6 days nor over 20 days,

the average interval between single exposures and onset of the disease being 11.8 days.

Infectious Period. Data concerning 49 cases which followed a limited exposure to a previous case are represented in Chart 1, as they afford an indication either of the earliest, latest or actual date with reference to the onset of the primary case when infection of the secondary case could have taken place. In 18 of these cases the first exposure (but not necessarily the last) fell, in all but 2, between the 4th day before and the 5th day after onset of the primary case; in all but 1 of the 49 cases the last exposure (not necessarily the first) was not later than the 5th day of the disease in the primary; and in 17 of the cases

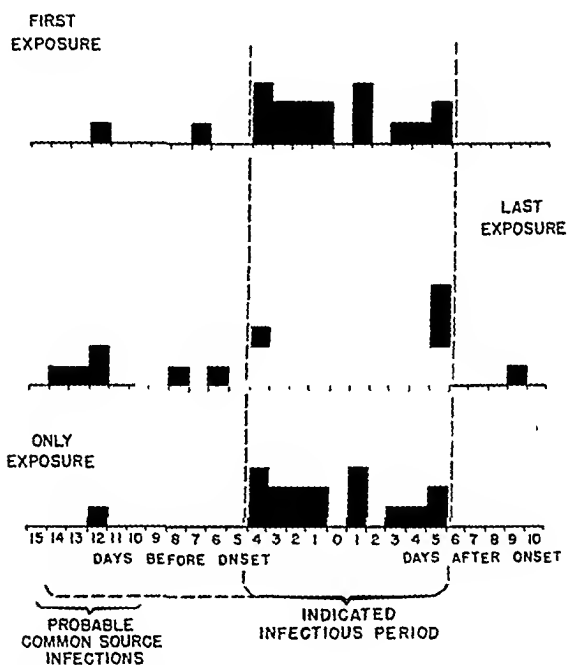


CHART 1.—Poliomyelitis. Cases following limited exposure to a previous case, according to day of disease when exposure took place.

there had been but a single exposure, in 16 it fell between the 4th day preceding and the 5th day following onset of the primary. In 5 of the 6 pairs of cases in which the last exposure to each other occurred earlier than the 5th day before the beginning of symptoms in the first case, the onsets in the 2 cases were practically simultaneous and occurred in both at an interval following the exposure to each other corresponding to the incubation period of the disease. These instances suggest that, as a group, the cases in which exposure took place upwards of 2 weeks before the onset of the first case represent, not secondary infection one from the other, but rather simultaneous infection from some uncovered common source at the time when the 2 individuals were in contact with each other (Table 1). Thus, in these exceptional instances

where the time of exposure to a previous case can be determined, an infectious period extending from 4 days before to 5 days after onset of symptoms is indicated.

TABLE 1.—POLIOMYELITIS. SIMULTANEOUS ONSETS IN CASES EXPOSED TO EACH OTHER MORE THAN 1 WEEK BEFORE ONSET, SUGGESTING SIMULTANEOUS INFECTION FROM A COMMON SOURCE

Exposure	Days before onset	Days, interval between cases
Last	14	1
	15	
Last	13	3
	16	
Only	12	2
	14	
Last	12	4
	16	
Last	8	9
	17	
Last	6	3
	9	

Incubation Period. The minimal, maximal and actual intervals between exposure and onset for the 49 cases are shown in Chart 2. In 18 of these cases, the maximal interval ranged from 6 to 14 days, and in 17 of these was the actual interval (following a single exposure).

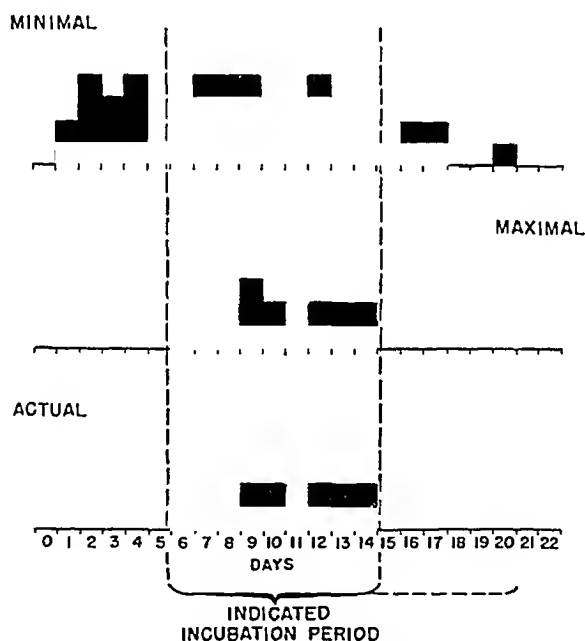


CHART 2.—Poliomyelitis. Intervals between exposure and onset (49 cases). Cases following limited exposure to a previous case, showing minimal, maximal and actual incubation periods.

The minimal interval ranged from 1 to 20 days; but in the 14 cases showing a minimal interval of under 6 days, the exposure was such that the incubation period could have been longer. Thus, the incubation period indicated by these intervals would appear to range from 6 to 14 days; and, exceptionally, to as long as 20 days.

Investigating an outbreak of 121 cases in Walker County, Alabama in 1941, Casey^{12,13} found 36 instances where the initial case in a neighborhood followed a single short visit (less than 48 hours) to or from a prior victim of the disease. In 30, the contact took place before the initial patient became ill, and in all but 3 before the 4th day of illness in the first case. The incubation period when plotted from the day of exposure to the onset of the prodromal period varied from 5 to 35 days, average, 12.8 days for 29 paralytic cases, and varied from 5 to 15 days, average, 9.5 days for the 8 abortive cases. Both the infectious period and the incubation period indicated by Casey's observations are in close agreement with those indicated by the cases presented in Charts 1 and 2.

From an earlier study of the intervals between multiple cases of poliomyelitis in families it was "inferred that the time of greatest infectiousness of infantile paralysis is probably at the beginning or within the first 3 or 4 days of the acute stage of the disease."⁵ In an ensuing comparison of multiple cases of measles, scarlet fever and poliomyelitis,⁵ it was pointed out, although this was not the main point of the study, that the range of time within which secondary cases of poliomyelitis occurred was of the same order as that in measles, which is clearly determined by its short infective period, but different from that of scarlet fever where the interval between cases is frequently longer, due, as is well known, to prolonged infectivity of the disease with complications.

Still another indication that sources of infection are of brief duration is seen in the succession of cases in small population groups in small geographic areas regardless of any traced contact relationship between them. While other factors appear to be major determinants in the occurrence of the recognizable disease in the few of the many exposed to the virus, the time of development of successive cases in a given outbreak is of course a reflection of virus dissemination in the population group. The occurrence of poliomyelitis in Vermont has been closely observed over a long period. Data are available on cases by townships and date of onset. In Chart 3 is shown the intervals in days between the onsets of the first and second, second and third, and the first and third cases in the same township, during the same year, for the period 1912-1926, irrespective of any actual contact relationships. The tendency to simultaneous onsets in the first and second and the second and third cases is interpreted as an indication that successive or adjacent cases tend to receive their infection from common sources—sometimes a previous recognized case, but more often an unrecognized source. There is the suggestion, furthermore, that these sources of infection tend to be of brief duration. The tendency to a longer interval between the first and third cases, an interval suggestive of the incubation period as previously shown, rather points to secondary infection. Since cases as early as the third in these local groups are already beginning to occupy the position of secondary infections (occurring frequently after an interval corresponding to the incubation period), it would appear that the dissemination of virus in a community is accomplished by successive virus reservoirs, each of short duration and each distributing virus to relatively small numbers of individuals. Such distributional features are those which would be expected in a

contact infection, propagated by a succession of infected individuals each remaining infectious for only a brief period during which transmission to a relatively small number of individuals occurs; but which would not be expected to result from grossly contaminated extra human reservoirs or from chronic carriers of virus.

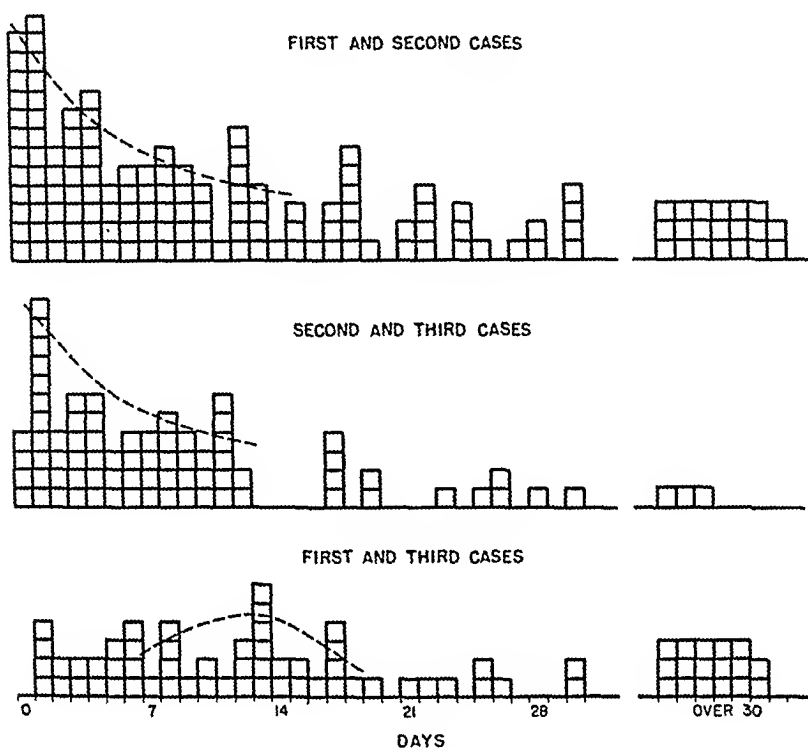


CHART 3.—Poliomyelitis. Intervals between adjacent cases (same township) irrespective of history of exposure.

Virus Detection. In many diseases deductions in regard to such features as routes of ingress or egress of the infectious agent, period of infectivity or healthy carriage, were made in the first instance from distributional features of the disease, and were later verified by virus detection. Thus, in typhoid fever it might be said that techniques for detection of the organism served more to clearly define epidemiologic features of the disease laid down by Budd without the aid of bacteriology, than to actually reveal them. On the other hand, there are examples where virus detection has been the point of departure in evolving epidemiologic concepts. Both are useful, but must be in accord.

Detection of an infectious agent in a given site does not in itself permit epidemiologic generalization. Brumpt¹⁰ and Davis^{15,16} showed that the ticks *Ornithodoros turicata* and *Ornithodoros parkeri* may harbor in their tissues for long periods certain infectious agents of which they are not known to be spontaneous transmitters. Parker²⁵ has used ticks of this genus as a means of transporting and storing safely for long periods the rickettsiae of Tobia petechial fever of Columbia and of South African tick-bite fever and the virus of spring-summer encephal-

itis of the U.S.S.R. More in point is the detection of hookworm eggs in the evacuations of patients which led Hirsch²⁰ to state, "... the mature eggs of the worm, on their discharge from the patient's intestine, undergo their first development in wet soil, being especially favored by high temperature; and thus the parasite comes in its larval stage, and doubtless by the medium of drinking water, into the human intestine, where it completes its development. We thus explain without difficulty how important for the occurrence of *cachexia aquea* are certain states of soil, and certain modes of life. . . ." This earlier concept is even more plausible when we consider that the larvae from soil (or water) are experimentally infectious by ingestion and do not have to undergo any cycle of development in the circuitous route to the intestine starting with ground itch, later brought in by Loos to correct the erroneous hypothesis.

In poliomyelitis, the proficiency of virus detection procedures is, because of technical difficulties, not exactly known. Furthermore, limited experience with it does not permit conclusions as to the relative frequency of the presence of the virus in one site or another. That the procedure as usually employed (the inoculation of single animals with suspected material) is deficient is indicated by the fact that intracerebral inoculation of emulsions of spinal cord from human cases (regarded as most favorable) frequently fails to produce the experimental disease. Flexner and Amoss^{19,28} pointed out that failure to incite infection in a single rhesus monkey does not indicate lack of power to infect other individuals of the same species. In our experience, single inoculations of this sort are successful in only about 50 % of instances, but a second inoculation of another or even the same animal with the same material frequently is effective. In view of such failures of virus containing material to infect, Flexner and Amoss^{19,28} concluded from the frequency with which they detected virus in nasal and pharyngeal mucosa of persons succumbing during the first week of the disease (and their failure to detect it in tissues surgically removed later) that during the first week or 10 days of the disease these tissues probably regularly contain the virus. Kling, Pettersson and Wernstedt²² had years earlier carried out a series of virus detection tests on 9 convalescents over a period of 7 months from which they concluded, "that the secretion from the mucous membranes of the mouth and intestines of persons who have recovered has had the power of infecting monkeys still several months . . . after the onset of the illness . . ." Flexner and Amoss felt that in interpreting the experiments of Kling, Pettersson and Wernstedt (done soon after poliomyelitis was first transmitted to an experimental animal when criteria for the experimental disease were not yet clearly established), it was necessary to take into account their qualifying statement that, "During the time occupied by the investigations, the virus had changed its character, so that it no longer caused inflammations with cellular exudations. Instead of this the degeneration of the nerve cells, the changes of the glia cells and the neurophagocytosis caused by the enlarged glia cells have been the characteristic changes. They have thus been of the same type as those appearing in the monkeys injected with secretions from abortive cases, and virus carriers, changes which . . . we consider ourselves justified in assuming to be due to a less virulent virus. The experiment also shows,

that the microbe rather quickly—already after 8-14 days—loses its power of causing inflammatory exudations in the inoculated animals. This fact is of very great importance from a practical point of view since it perhaps gives us the right to assume that the virus, possibly rather soon after the termination of the acute stage, gets weaker.” Using the more rigid criteria of infection in the monkey which had come to be accepted, the virus detection experiments of Flexner and Amoss indicated brief rather than chronic carriage of the virus in the nasopharyngeal mucosa.

The dominant concept of the epidemiology of poliomyelitis, to the effect that the virus is disseminated through direct contact, receiving its major contributions from Caverly, Wickman, Flexner and Frost, and their coworkers, has been challenged at each step in its advancement by hypotheses either containing some element of plausibility or of hope. The water-borne theory, originating largely in supposed associations in time with swimming, or in space with water courses, has again been brought to the fore by the unmistakable detection of the virus in intestinal discharges. Virus has been detected in the stools of cases, contacts of cases and of other individuals as well as in sewage coming from hospitals in which there were cases of poliomyelitis and even in sewage draining cities in which cases of the disease either were numerous or few. Furthermore, it has been shown experimentally, that the virus resists chlorination in the doses ordinarily used in the treatment of water supplies. Thus, these laboratory findings in themselves lend plausibility to the theory of transmission through water. To many (to paraphrase the reaction to a similar situation where a laboratory discovery led to the rejection of a large accumulation of evidence for the theory which it opposed), “this threw a flood of light on the etiology . . . and revolutionized our entire conception of its epidemiology by displacing the then dominant and paralyzing . . . theory of its origin by the now generally accepted and more hopeful . . . one.”* Maxcy²⁴ in a recent “dissection” of the question has pointed out that in spite of laboratory data, the pattern of spread does not suggest dissemination through water supplies. No epidemics have been encountered having the well-known characteristics of water-borne disease, and the tendency to radial spread is not influenced by water supplies in the areas involved.

Renewal of studies, under circumstances which have permitted far more extensive laboratory investigation than was possible in the period of small scale experimentation, when attention was centered on detection of virus in nasopharyngeal secretions, have amply confirmed the presence of the virus in intestinal discharges. The detection of virus in intestinal discharges from cases of the frank disease and suspected abortive cases, in the acute stage and in convalescence, in healthy contacts, as well as in sewage, by Paul and Trask has been confirmed by numerous workers in many localities. In the course of virus detection

* A statement of Rogers and Muir²⁶ concerning the discovery of the Hansen bacillus in 1873 in leprosy and the theory of heredity which had prevailed since the epidemiologic studies of Danielson and Boeck in 1848. Subsequent studies indicate that the complete acceptance of the contagionist view does not take into account familial aggregation in the occurrence of the disease which has been interpreted as a manifestation of hereditary susceptibility to infection.^{1,2,6,9}

studies in New York City sewage, Trask and Paul²⁹ incidentally readily demonstrated the presence of tubercle bacilli in sewage. They state, "Certain monkeys, inoculated intra-abdominally with the routine dose of 20 cc. of etherized unconcentrated sewage, contracted an unusual form of peritoneal tuberculosis whereby, 6 to 12 weeks after inoculation, the omentum and visceral peritoneum were found studded with tubercles of fairly uniform size while lungs, pulmonary nodes, liver, spleen, and kidney were relatively free . . . this form of tuberculosis was common. In fact, in monkeys observed for 6 weeks or more, it was seen in all of 7 monkeys so inoculated. From 1 of them a strain of tubercle bacillus was recovered which was identified as of human type by its growth in the presence of glycerol and its pathogenicity for guinea pigs and relative lack of pathogenicity for rabbits." They also point out that their methods were highly selective in that systematic observations of their animals were limited to body temperature, to general features, to the function of motion, and to the histology of the cord and brain stem. "Thus pathogenic bacteria, measles, mumps, etc., could have infected our monkeys [from inoculation of sewage] without our knowing it." In spite of these observations, no one has felt it necessary to recast the epidemiology of tuberculosis.

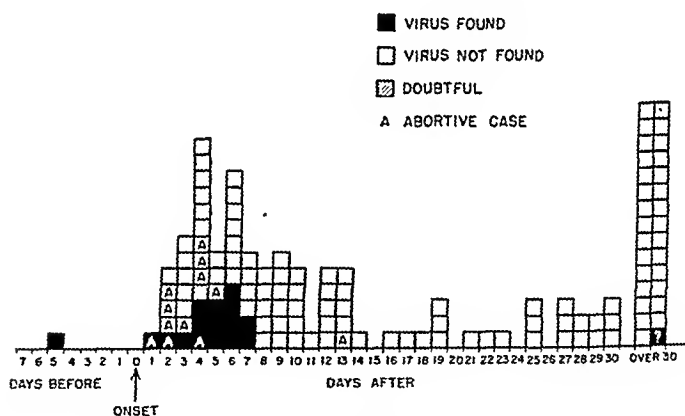


CHART 4.—Poliomyelitis. Detection of virus in nasopharyngeal tissues and secretions, according to day of disease.

Thus, there can no longer be a difference of opinion regarding the presence of the virus of poliomyelitis in both nasopharyngeal and intestinal discharges. But there remains the question of their relative importance in the widespread dissemination of the virus.

Because of the meagerness of data, and the lack of criteria of reliability of the procedures for virus detection, the relative frequency with which virus appears in the nasopharyngeal or intestinal discharges cannot be stated. In Charts 4 and 5 are shown the results of a number of virus detection tests carried out with nasopharyngeal and intestinal secretions from patients with poliomyelitis, according to the day of the disease. These have been gathered from the literature available, with no attempt at completeness. In a number of papers, information was incomplete and negative tests were not included, so that no con-

clusion can be drawn as to the actual frequency with which virus was detected. But in one respect there is an essential difference. The virus has been detected in the nasopharyngeal secretions, in spite of a relatively large number of tests late in the disease, only within 7 days of the onset, with a single exception (in 1912) the interpretation of which is not entirely clear. On the other hand, the data available indicate that virus detection in intestinal discharges is relatively easy, weeks or even months after onset of the disease. Thus, from these laboratory observations alone one might be led to postulate 2 mechanisms of spread, the operation of one resulting in outbreaks of the general character of those seen in measles for example, and the other producing a pattern of distribution like that of typhoid fever.

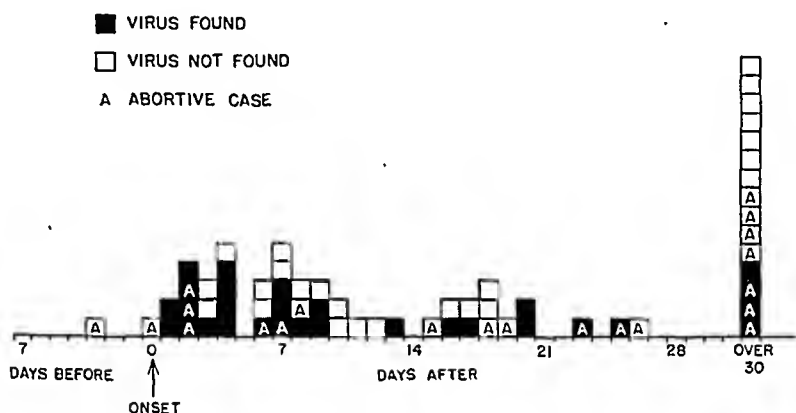


CHART 5.—Poliomyelitis. Detection of virus in intestinal discharges, according to day of disease.

The classic example of 2 patterns of the same disease is seen in plague where different virus reservoirs set up mechanisms resulting not only in 2 different patterns of distribution but in different clinical types of the disease. There are numerous examples where different mechanisms of dissemination of the same infectious agent result in clearly distinct epidemiologic patterns, as in tularemia spread by handling rabbits or transmitted by ticks.

In still other diseases seemingly with potentialities for more than one mechanism of dissemination, it may be difficult, on the surface at least, to explain why they (as judged by patterns of distribution) restrict themselves to one particular means of dissemination.

Poliomyelitis preponderantly follows a single pattern of distribution, as measured by general features of the disease, such as seasonal and age distribution, as well as by time and space relationships between cases. This pattern, with the evidence that subclinical infection is the rule and frank disease the exceptional outcome of exposure to the virus, is consistent with the view that the virus spreads directly from person to person each in his turn playing the part of a brief carrier. Exceptions are rare. A few outbreaks of different pattern have been encountered in which the evidence indicated transmission through milk supplies briefly contaminated with the virus.^{3,17,23} In 1 of these, where a source of infection of a small milk supply could be traced,²³ the explosive outbreak occurred at an interval corresponding with the incubation period

of the disease following the consumption of milk drawn by a patient in the first 3 days of the disease. The particular point in the present connection illustrated by this outbreak is that the source of infection was an acute case and not a chronic carrier. Similar outbreaks, attributable to chronic carriers of the virus, which might be expected on the basis of virus detection studies alone, have not been observed. Still another localization in occurrence is seen in bulbar poliomyelitis following tonsillectomy or adenoidectomy.^{4,8,18} Here the nasopharynx (upper respiratory or upper gastro-intestinal) and not the lower respiratory or lower gastro-intestinal tract is implicated.

Just a century ago, in this Journal, Colmer¹⁴ under the title "Teething Paralysis in Children" described a group of cases in the parish of West Feliciana, Louisiana, now considered the first reported outbreak of poliomyelitis in this country. Little epidemiologic detail was given beyond the facts that the 10 or 11 cases all occurred in young children, in the summer and fall and within a short space of time and distance. Since Colmer's report many epidemiologic studies have established these as cardinal features of the pattern of distribution which is everywhere characteristic of the disease. In this paper a number of features of distribution are reviewed which implicate brief harborage of the virus, as has been demonstrated in the nasopharynx, rather than chronic harborage as demonstrated in intestinal contents. In exceptional occurrences, with different patterns of distribution, either the nasopharynx or a short period of infectivity are likewise indicated.

As already discussed, no satisfactory deductions can be made from reports in the literature concerning the relative frequency with which poliomyelitis virus has been detected in the nasopharynx and intestine. In the early work, Kling, Pettersson and Wernstedt²² tested both sites. Although they reported detection of virus both in nasopharynx and intestine in a high proportion of cases as well as in healthy contacts, it is difficult, because of the criteria used for infection in their inoculated animals, to form an opinion from reading their published protocols as to the actual frequency with which virus was detected in either. In a recent survey of healthy harborage of the virus, Kessel and Moore²¹ examined 136 individuals admitted to hospital for tonsillectomy. Stools and the excised tonsils were obtained on the same day and made into pools (usually of 3 individuals). Of the 49 tonsil pools, 5 contained virus and 1 stool pool was positive, being from the same patients furnishing one of the positive tonsil pools. It can be stated, therefore, that in this survey at least (because of pooling) 5 out of 136 individuals harbored poliomyelitis virus in tonsils and at least 1 out of 136 also harbored virus in the intestine. The relation of this substantial healthy carrier rate to the prevalence of the disease in the locality, will appear in the detailed report of these observations.

W. LLOYD AYCOCK, M.D.
JOHN F. KESSEL, M.D.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF JANUARY 19, 1943

Effect of Diet and Food Intake on Response of Mice to Murine Poliomyelitis Virus (Lansing Strain). CLAIRE FOSTER, J. H. JONES, WERNER HENLE and FRIEDA DORFMAN (Departments of Pediatrics and Physiological Chemistry, University of Pennsylvania and Children's Hospital). Young mice (284) approximately 30 days old were divided into three groups of 57, 170 and 57 animals respectively. Group I received a complete synthetic diet, and Groups II and III the same diet, except that it was deficient in vitamin B₁. When the animals of the last two groups showed definite signs of vitamin B₁ deficiency, the amount of thiamin was increased, and thereafter varied in an attempt to maintain the majority of these animals alive and at approximately constant weight. Shortly after the first adjustments in thiamin were made, all the animals were injected intracerebrally with 0.03 ml. of mouse brain suspension in saline. Groups I and II received brain infected with the Lansing strain of murine poliomyelitis virus and Group III normal brain. At the 12th, 21st and 46th days after inoculation the percentage incidence of death and paralysis in the various groups was as follows: Group I, deaths—85, 95 and 96; paralysis—72, 80 and 81. Group II, deaths—19, 43 and 69; paralysis—7, 24 and 41. Group III, deaths—10, 14 and 19; paralysis—none at any time.

Another experiment, with 179 mice, was conducted very similarly to the above except that Groups II and III were also given the complete diet but restricted to 1 gm. of food per day (about 40% of normal

intake). The percentage incidence of death and paralysis at the 12th and 21st days was as follows: Group I, deaths—100 and 100; paralysis—86 and 86. Group II, deaths—21 and 68; paralysis—13 and 47. Group III, deaths—26 and 44; paralysis—none at any time. The amount of virus given in the first experiment was from 10 to 100 and in the second, 500 to 1000 50% mortality doses.

It is clear that a deficiency of either vitamin B₁ or of total food intake definitely delays the action of poliomyelitis virus in mice. Experiments also indicated that a simple caloric deficiency produced similar results, and the administration of large amounts of thiamin when the food intake was reduced did not alter the results.

Hypertension Following Chronic Lead Poisoning: Experimental Study. J. Q. GRIFFITH, JR., and M. A. LINDAUER (Robinette Foundation and Medical Clinic, University of Pennsylvania). Fifteen albino rats were given 70 mg. of lead as a soluble salt daily for 6 days each week. The lead was introduced in 2 cc. of water by stomach tube. Blood pressure was measured at varying intervals. A few animals developed a vascular hypertension by the 12th day, and all that survived the 36th day were hypertensive. Based upon measurement of plasma creatinine in 4 animals, it was suggested that there was associated renal damage.

A Further Study of the Effect of Vagotomy on the Secretory Response of the Pancreas to Peptone. J. O. CRIDER and J. E. THOMAS (Laboratory of Physiology, Jefferson Medical College of Philadelphia). In a previous communication (*Proc. Physiol. Soc. of Phila.*, 17, 6, 1941-1942), we reported that cutting or cocainizing both vagus nerves was followed by disappearance of the secretory response of the pancreas to intra-intestinal administration of peptone. These results were obtained in semiacute experiments in which the observations were made within a short time after the nerves were blocked or cut. In experiments performed since then in collaboration with Dr. A. J. Ramsay, it has been found that: 1. Administration of peptone into the intestine over a period of several hours causes changes in the acinar cells of the pancreas which are indistinguishable from changes that follow prolonged stimulation of the vagus nerves.

2. Twenty-four hours after cutting the vagi, peptone in the intestine is without effect on the histologic appearance of the pancreatic cells.

In experiments continued over a longer period of time following vagotomy we have found that the capacity of the pancreas to respond to peptone stimulation recovers to some extent. The recovery is incomplete in that the volume, specific gravity and total nitrogen of the secretion obtained following a standard dose of peptone are less than normal and the latent period is prolonged. Although the concentration of the secretion as indicated by the total nitrogen in mg. per cc. is reduced only slightly, the total amount of nitrogen (N per cc. \times vol.) in each sample collected following administration of a standard dose of peptone after vagotomy is only a little more than one-half the normal

amount. The nitrogen content is, however, still several times as great as in a corresponding volume of secretion obtained in response to secretin or to HCl stimulation.

These results require modification of our previous conclusion to the effect that the reaction of the pancreas to peptone is a vagal reflex. Although the vagi are evidently involved in the response in the normal animal an additional mechanism, the nature of which has not been determined, must be taken into account.

Electron Microscope Studies of Bacteriophage. THOMAS F. ANDERSON (The Johnson Foundation for Medical Physics, University of Pennsylvania). The bacteriophages are the only class of viruses whose mode of action on susceptible cells (bacteria) can so far be studied in detail with the electron microscope. Recent work (S. E. Luria and T. F. Anderson, *Proc. Nat Acad. Sci.*, 28, 127, 1942; S. E. Luria, M. Delbruck and T. F. Anderson, unpublished) has made it possible to identify the phage particles as tadpole-shaped bodies with heads ranging from 50 to 80 m μ in diameter and tails of varying dimensions, and a morphology which is characteristic of the strain of phage. They are readily adsorbed on susceptible bacteria, and upon lysis of the bacterium appear to be liberated from *within* the bacterial cell. The débris of cells of *E. coli* lysed by one strain of phage contains no particles which could be mistaken for particles of the other phage to which the bacterium is susceptible.

More recent work indicates that the activity on *E. coli* of gamma-phage is rapidly destroyed by intense sonic vibration of the phage suspension. At the same time electron microscope studies show that the tadpole-shaped particles of gamma-phage are disintegrated by sonic vibration to a corresponding degree. This observation can be taken as further indication that the lytic activity of phage is connected with the tadpole-shaped particles

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of “milligrams per cent”—is well covered on Page 53 of the American Medical Association's book entitled “Medical Writing”: “Results of chemical determinations are frequently expressed as ‘milligrams per cent’ or ‘grams per cent.’ This means literally ‘milligrams (or grams) per hundred milligrams (or grams),’ which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as ‘milligrams per hundred cubic centimeters’ or ‘milligrams per 100 gm.’ If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply ‘per hundred cubic centimeters’ the first time the phrase appears and to use merely ‘milligrams’ (not ‘milligrams per cent’) thereafter.” We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word “consider” as indicating that the item is still under consideration or being meditated upon, *i. e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as “think to be,” or “regard as” or “believe to be” or “hold as an opinion” gives the more exact meaning.

THE EDITOR.

THE
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APRIL, 1943

ORIGINAL ARTICLES

DISTRIBUTION OF THE PATTERNS OF VENTRICULAR
POTENTIAL WHICH DETERMINE THE FORMS AND
SIGNIFICANCE OF ELECTROCARDIOGRAMS

BY CHARLES C. WOLFERTH, M.D.

MARY MILLER LIVEZEY, M.D.

AND

FRANCIS CLARK WOOD, M.D.*

PHILADELPHIA, PA.

(From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the
University of Pennsylvania)

WE have recently reported² observations concerning the distribution of potential of ventricular origin on the body surface which demonstrate that two patterns of potential variation, one of which can be recorded when an exploring electrode is placed on the anterior chest wall just to the right of the heart, and the other, just to the left of the heart, are each well preserved along a surface line to the homolateral shoulder tip. It was found, however, that decrement (*i. e.*, diminution in magnitude of potential variation) occurs as distance from the heart increases. Because of these characteristics, it was possible to demonstrate certain relationships of potential among groups of positions along each of these lines. Thus, groups of three positions can be found whose relationship is such that the ventricular potential of an intermediate position is approximately equal to the mean potential of a proximal and distal position, despite the fact that there may be considerable difference of potential between the two latter positions. Moreover, groups of three positions can be found along each of these lines whose relationships

* Now on leave of absence "on active service."

indicate either that the potential variations of the proximal position are approximately equal to the sum of the potential variations of the two distal positions from an assumed base line of zero potential at every instant of the ventricular cycle, or that each position in such groups includes the same pattern of unrecognized potential variation. The improbability of the latter alternative has been pointed out.

In our former paper we designated these two patterns which could be traced far from the precordial region (Fig. 1) either by pairing electrodes at appropriate positions along each line or by the method of balanced potentials, as the " C_1 pattern" and the " C_5 pattern,"

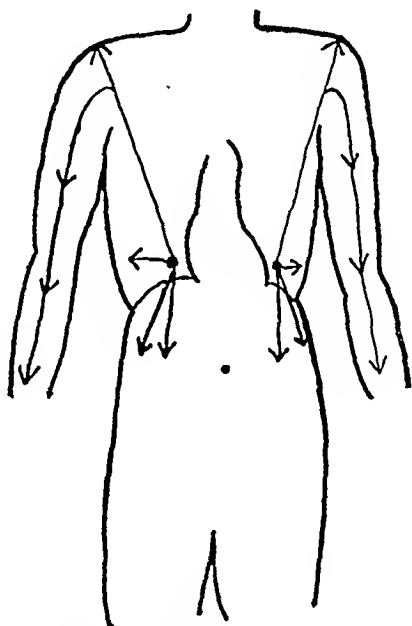


FIG. 1.—Diagram indicating by lines and arrows the directions along which distribution of the C_1 and "extra-apical" patterns of potential can be demonstrated.

using the conventional meanings attached to the C_1 to C_6 positions (across the precordium from right to left). It was pointed out that the C_1 pattern sometimes remains intact as near to the heart as the C_2 position and can be recognized as far from the heart as the right arm or tip of the right shoulder, unless decrement is so great that potential variations become quite small at the distal areas. Under such circumstances even slight technical errors which remain constant assume greater relative importance, so that they may distort the recorded pattern and mask the relationship. Moreover, it should be emphasized that minor modifications in pattern are to be expected, since these regions are not insulated from the remainder of the body. The " C_5 pattern" is usually well maintained on the

left side, so that it is easily recognizable as far away as the left arm and left shoulder. The term "C₅ pattern," however, is an unsatisfactory designation since the location of the position on the left chest wall which fulfills these relationships is not always the C₅ position. This is probably due in part to differences in anatomic relations of the left border of the heart to the chest wall. The position is usually found just outside the left border of the heart somewhere between the C₄ and C₆ positions. Occasionally, however, the pattern found over the arm and shoulder is not fully maintained as low as the level of the C positions, but is maintained to a level 1 inch or 2

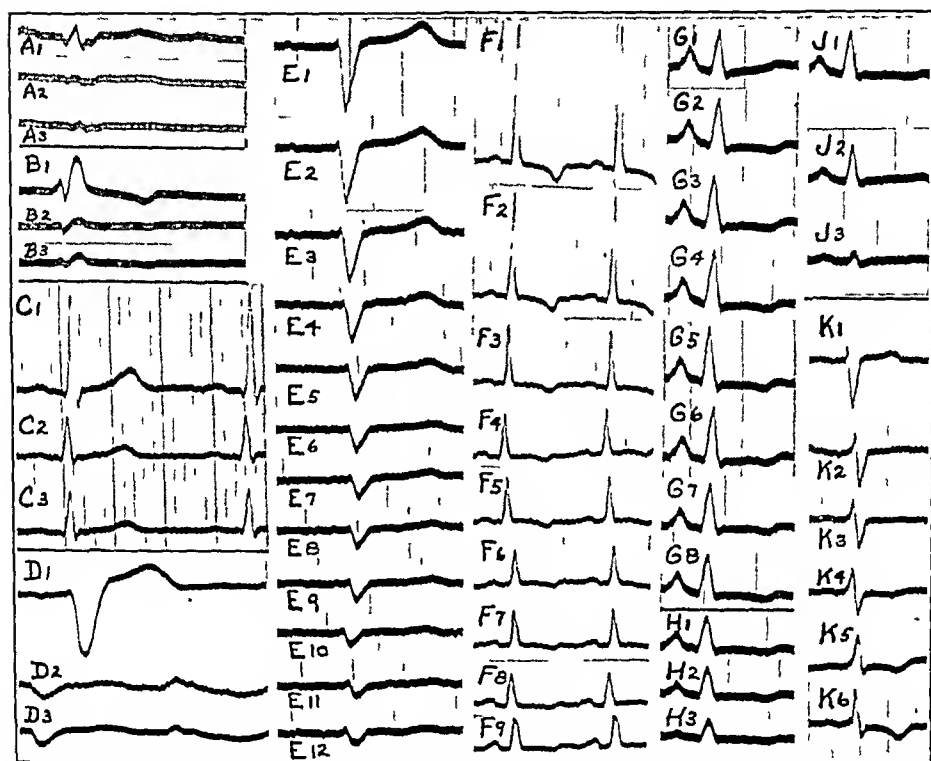


FIG. 2.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

higher. For these reasons we have abandoned the term "C₅ pattern" for the more accurate although less convenient designation "extra-apical pattern." The similarity of the C₁ and right arm patterns, and of the extra-apical and left arm patterns was shown in the paper mentioned, but can be demonstrated in a more striking way by adjustment in sensitivity of the galvanometer so that the amplitude of the deflections recorded at the C positions is comparable with that of the arms (Fig. 2, A, B, C and D). It was shown that Lead I is formed almost entirely by the extra-apical pattern, subject to the decrement found in the left arm, minus the C₁ pattern subject to the decrement found in the right arm.

The studies which formed the basis of the previous report suggested that, aside from the patterns found on the precordium inside and exclusive of the C_1 and the extra-apical positions and adjacent areas above and below, there are but three major patterns of potential variations on the body surface which can be detected by electrocardiography. In certain areas, however, particularly about the attachment of the diaphragm, there may be sufficient overlapping in the distribution of these patterns to result in composite configuration. The three major patterns are: (1) the C_1 , and (2) the extra-apical patterns mentioned above, and (3) a pattern found by the method of balanced potentials when the exploring electrode is placed anywhere on the body below the attachment of the diaphragm to the trunk, except on the abdominal wall near the precordium. This third pattern which because of its distribution we have called "the diaphragmatic pattern," unlike the other two, does not seem to be subject to rapid decrement on the body surface as distance from the heart increases, but is often found to be much the same in areas far distant from each other and at variable distances from the heart (Fig. 2, $G1-8$).

The method of balanced potentials previously described was used in the major part of this study dealing with patients. Observations were made on a large number of cases with common types of electrocardiographic abnormality such as those caused by ventricular hypertrophy, the various types of infarction, and bundle branch block.

1. *Distribution of the C_1 Pattern.* As stated above, in some cases the C_1 pattern remains intact as near the ventricles as the C_2 position. As the exploring electrode is moved to positions along a surface line from the C_1 position to the tip of the right shoulder, the pattern is well maintained as distance from the C_1 position increases, until the deflections become extremely small (Fig. 2, $E1-7$). Sometimes the pattern can still be recognized at the tip of the shoulder (Fig. 2, $E8$). The deflections obtained on the right arm are always smaller than those of the anterior axillary region and always larger than those obtained at the tip of the shoulder. Although the matter has not been fully studied, various positions on the right anterior and lateral chest wall at some distance from this line may also yield much the same pattern. If a surface line is drawn across the right side of the back from the tip of the right shoulder to the diaphragmatic level, at a point midway between the spine and the posterior axillary border, and the exploring electrode placed at various areas along this line, the results are as follows: the deflections grow smaller between the tip of the right shoulder and the spine of the scapula (Fig. 2, $E8-11$). At the latter area they are usually smaller than at any other area on the body surface. As the exploring electrode is carried down the back toward the diaphragm, larger deflections having the C_1 pattern are sometimes found but near the dia-

phragm the C_1 pattern tends to be lost. This finding will be referred to later as well as the distribution of the C_1 type of potential on the abdomen.

2. *Distribution of the Extra-apical Pattern of Potential.* The distribution of the extra-apical pattern of potential on the left chest, shoulder and arm is very similar to that of the C_1 pattern on the right side. The most convenient method that we have discovered for finding it in a position near the heart is the following: Tracings are made by the method of balanced potentials with the exploring electrode on the left arm and then on a series of 5 evenly spaced areas along the line between and including the C_4 and C_6 positions. From one or more of these positions a pattern can be obtained, which so far as our experience goes always resembles that of the left arm. Occasionally, however, as has been stated, the *closest* resemblance cannot be found at this level, but may be found 1 inch or more above the level of the apex along the line from a position just outside the apex to the tip of the left shoulder. As the exploring electrode is carried along this line to various areas nearer the shoulder, decrement may not begin to manifest itself until the electrode position is at least 2 or 3 inches above the level of the apex. Above this area decrement is rapid as distance from the heart increases, although the deflections are usually fairly large at the tip of the left shoulder (Fig. 2, *F1-6*). The extra-apical pattern is well maintained there, unless because of some pathologic condition deflections had been small at the extra-apical position and are therefore extremely small at the tip of the shoulder. With this exception the amplitude of deflections obtained with the exploring electrode on the left arm is usually considerably greater than in the case of the right arm. If a surface line is drawn from the tip of the left shoulder posteriorly to the level of the diaphragm about midway between the spine and the left posterior axillary line (similar to the line described on the right side) and the exploring electrode placed along this line, the findings are as follows: the extra-apical pattern may undergo further decrement at areas along the line to about the level of the spine of the left scapula (Fig. 2, *F6-9*). When potential variations are small at the extra-apical position, they are almost negligible over the spine of the left scapula, often being even smaller than on the right side. Below the spine of the scapula there may be little or no further decrement and the amplitude of deflections may actually increase. However, as the diaphragmatic level is approached the pattern may show considerable change, as it does on the right side.

3. *The Diaphragmatic Pattern of Potential.* The diaphragmatic pattern can be recognized in tracings made by the method of balanced potentials whenever the exploring electrode is placed on the parts of the body surface below the level of the diaphragm posteriorly, on the right flank below the diaphragm, the left flank below

the diaphragm (unless the heart extends well toward the axilla), the lower abdomen and both legs. The deflections as a rule do not vary much in amplitude in these areas, thus failing to show the marked decrement observed in the two other patterns, as distance from the heart increases (Fig. 2, *G1-8*). On the right side of the back, rapid decrement of the diaphragmatic pattern is observed as the electrode is moved to positions successively higher above the attachment of the diaphragm so that deflections decrease and the pattern may be gradually lost in the course of a few inches (Fig. 2, *H1, 2* and *3*). On the left side, however, the extra-apical pattern is usually so well transmitted to the back above the diaphragm that a similar observation cannot be made and the attachment of the diaphragm often marks an almost abrupt transition from one pattern to the other (Fig. 2, *K1-6*). However, in certain cases with small deflections at the C_5 position, decrement is such that these latter potential variations may become negligible on the back of the chest. Under such circumstances the rapid decrement and loss of the diaphragmatic pattern of potential above the attachment of the diaphragm can be demonstrated just as it can be on the right side (Fig. 2, *J1, 2* and *3*).

4. *Precordial Potential Patterns Between the C_1 and Extra-apical Positions and Their Distribution.* It is well known that, as an exploring electrode is moved from the C_1 position to successive C positions to the left, and tracings made at each of these areas, the pattern tends to show at least some change, so that no two are exactly alike. If a definitely pathologic pattern is recorded at one of these areas, it is also reflected at least to some extent at nearby areas. When marked differences are recorded from adjacent C positions, a series of tracings made from areas between the two shows the change to be gradual rather than abrupt (Fig. 3, *B1-5*). Special methods of pairing electrodes are not required to demonstrate these phenomena. They suggest that there is considerable overlapping of the cardiac volumes which contribute most of the potential to precordial surface areas near each other.

If, in the study of the various precordial potential patterns, the method of balanced potentials is used, or the exploring precordial electrode is paired with an electrode on an area of relatively slight potential variation such as the right scapular region,* and an arbitrarily chosen test lead is simultaneously recorded for the purpose of timing the deflections found in each position with reference to those of other precordial positions, the following facts can be demonstrated: (1) potential variation seems to begin at the same instant on every part of the precordium (Fig. 3, *A1-5, D1-5*,

* The patterns obtained by these methods of pairing do not differ materially from those obtained by pairing the exploring electrode with one placed on the right arm unless there is considerable difference of potential between the right arm and the right scapular position. Even in such cases the C_1 and C_2 patterns remain practically intact although the amplitude of deflections may be less in the CR leads.

Fig. 4, A1-5), although occasionally in certain areas there may be a close enough balance of electromotive forces that our relatively crude methods of recording may fail to show potential variation. (2) Over normal hearts, at the C₁ position there is an initial positive potential variation of relatively small magnitude, terminated by a sharp wave of negativity. As the exploring electrode is moved to the C₂, C₃, C₄, C₅ and C₆ positions successively, the positive potential tends to increase in magnitude with each shift in position as far to the left as the C₄ or C₅ position (depending upon the relation of the cardiac apex to the chest wall) but in all these positions it is terminated by a sharp change in direction of potential variation (Fig. 3, A1-5). These waves, as has been pointed out by Wilson

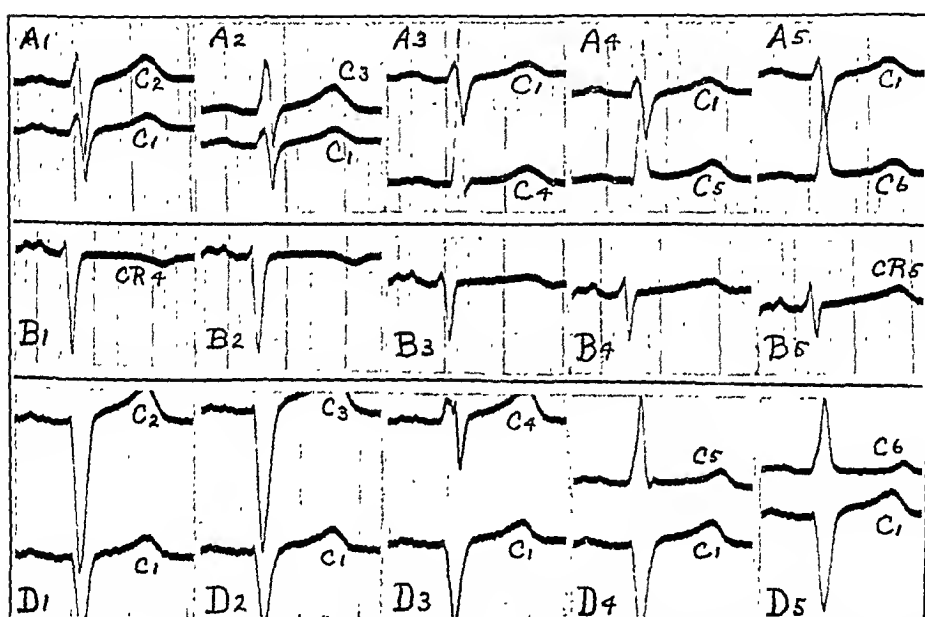


FIG. 3.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

using a different method,¹ seem to correspond to the pre-intrinsic and intrinsic waves of epicardial electrograms. In certain cases initial negative potential of small magnitude may be found at the C₄ or C₅ position. When it is found at the C₄ position, its magnitude is usually slightly greater at the C₅ position. In such cases there is delay in the onset of positive variation at the positions where potential variation is initially negative. The T wave potential variation is normally positive at all the C positions to the left of the sternum. Thus with such methods of pairing electrodes, problems of standardization become relatively simple. (3) When notching or splintering of the QRS complex is present, suggesting that two pairs of pre-intrinsic and intrinsic-like waves are being recorded at slightly different time intervals, it can sometimes be shown that one of these

pairs shows maximum deflections at the C_1 or C_2 position and the other at the C_4 , C_5 or C_6 position (Fig. 3, $D1-5$, Fig. 4, $A1-5$). This indicates that they are derived from different parts of the heart.*

We have previously shown that the C_1 and extra-apical patterns are distributed over the anterior abdominal surface although with considerable decrement as distance from the heart increases.² It can be shown by the same methods used to demonstrate the distribution of the C_1 and extra-apical patterns, that the patterns found at intermediate C positions are also distributed on the surface of the upper abdomen, although this relationship is somewhat obscured by the overlapping in distribution of neighboring chest patterns (Fig. 3).

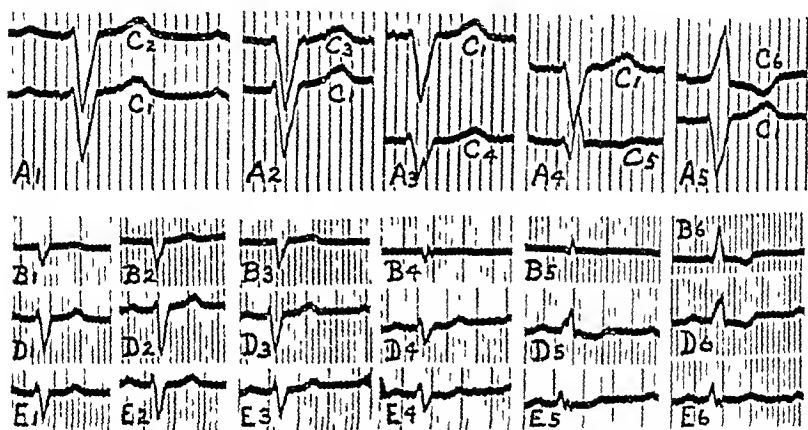


FIG. 4.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

Studies on Experimental Animals. Observations on the rat showed that the ventricular potential of all parts of the body below the diaphragm, including the hind legs, abdominal wall, liver and intestine, is about the same (Fig. 5). This obviously means either that potential is almost uniformly distributed in this part of the rat's body, or that these tissues are almost insulated from cardiac electrical activity.

The distribution of ventricular potential was next investigated in a medium-sized dog, using needle electrodes insulated except at the tip. Nembutal anesthesia was employed. When the exploring electrode was paired with an electrode inserted beneath the skin of the right foreleg, tracings practically identical in pattern were obtained from both legs, various parts of the abdominal wall and corresponding points within the abdomen reached by puncturing through the abdominal wall (Fig. 6, $A1-8$). However, the deflections became progressively slightly larger as the exploring electrode was placed higher on the abdomen and were larger in the subcostal angle than elsewhere on the surface, indicating the presence of decrement as distance from the heart increased. From the mid-abdomen to the subcostal angle the deflections obtained by puncturing the exploring

* Observations on the contribution of each ventricle to the electrocardiogram will be presented in a subsequent paper.

électrode through the abdominal wall were slightly although appreciably larger than those obtained from the corresponding surface area.

When the abdomen was opened and the exploring electrode inserted directly on the diaphragm, practically the same pattern was recorded everywhere except near to and directly under the heart (Fig. 6, *B1-7*). This pattern was like the one recorded from the legs, the abdominal wall and within the abdomen. However, as the exploring electrode was moved from various parts of the periphery of the diaphragm to positions nearer the heart, much greater increase in amplitude of deflections was observed than had been found by moving the electrode comparable distance on the abdomen. Near to and directly under the heart, not only were the deflections larger than elsewhere but also as the electrode was moved from one

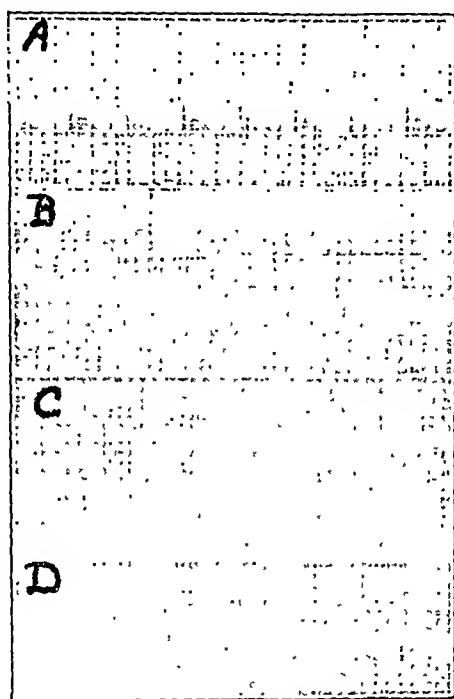


FIG. 5.—A series of electrocardiograms made in a rat. In *A* the tracing was made with electrodes paired on the left hind leg and right fore leg with the polarity as in Lead II. In *B* the left leg electrode was shifted to the abdominal wall, in *C* to the surface of the liver, and in *D* to the surface of intestinal loops. Note the similarity of pattern and size of deflections in all these tracings.

position to another, the patterns changed materially. Examination of the configuration of T waves in the patterns found near the heart suggested that the potential of the diaphragm at all positions farther from the heart was in effect a composite of these proximal patterns. It would appear, therefore, that the potential of all parts of the body below the diaphragm was derived from the same sources as the patterns found on the diaphragm. Furthermore, it would appear that: (1) decrement in potential on the diaphragm was considerable as distance from the heart increased; (2) it was proportionately less rapid although still appreciable on the upper abdomen; and (3) below the mid-abdomen further increase in distance from the heart caused practically no change in magnitude of deflections.

When the exploring electrode was inserted upward through the dome of the left diaphragm, the pattern obtained from a position just above the

diaphragm was much the same as that found on the corresponding under surface although the QRS complex deflections were larger and the T wave smaller (Fig. 6, *B6* and *C1*). As the electrode was pushed upward into the left lung and tracings were made at intervals of about 1 cm., gradual change

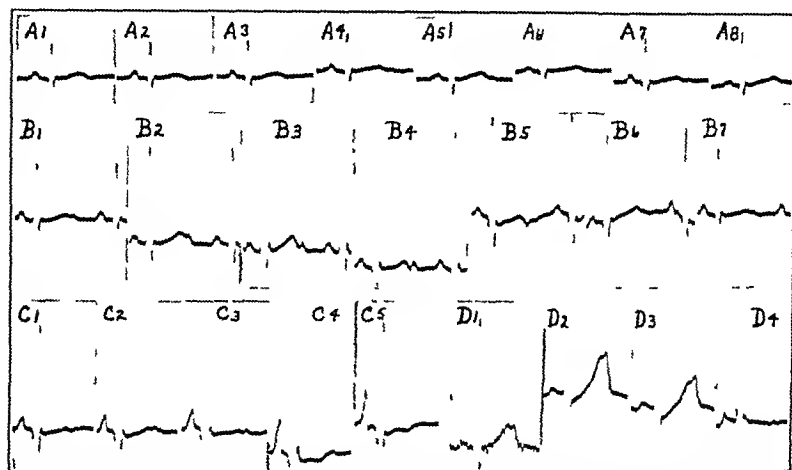


FIG. 6.—Electrocardiograms under various conditions illustrating distribution of potential in the dog (See explanation in text, section preceding Summary.)

in pattern occurred in the lower 3 cm. of the lung (Fig. 5, *C1-5*). When the exploring electrode was pushed through the dome of the right diaphragm and the same procedure followed, the differences in pattern were

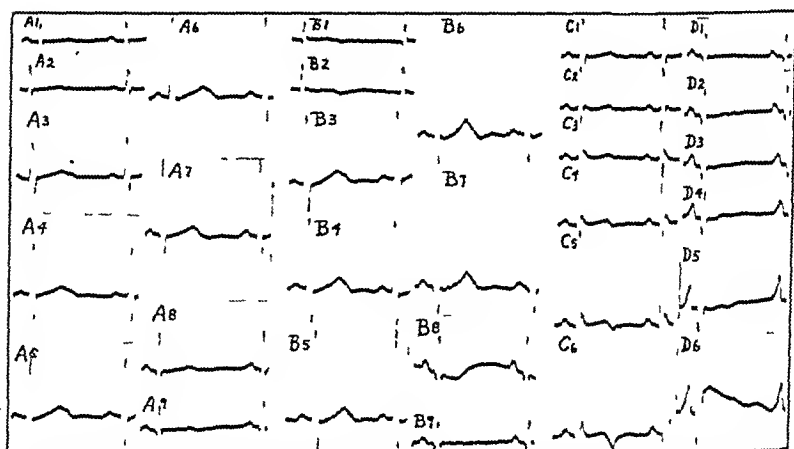


FIG. 7.—Electrocardiograms under various conditions illustrating distribution of potential in the dog (See explanation in text, section preceding Summary.)

slightly greater than had been found on the left side (Fig. 6, *D1-4*). It is possible, however, that the electrode was nearer the heart on the right side. In this series of experiments, the exploring electrode was probably never less than 3 cm. nor more than 5 cm. distant from some part of the external

surface of the heart. It was evident that considerable potential variation develops within the substance of both lungs and that the potential of areas near to the heart and to each other may differ considerably.

Study of the patterns obtained when the exploring electrode was placed on the chest wall suggested that decrement occurred as distance from the precordium increased, in somewhat the same manner as in the human (Fig. 7, *A1-9*). However, considerable change in pattern was noted at areas distant from the heart. We have made no attempt to develop the method of balanced potentials in the dog and have therefore not ruled out the possibility that these changes in pattern are due to the relatively greater influence of the right foreleg potential variations on the configuration of electrocardiograms when the exploring electrode is placed at some distance from the precordium.

When the exploring electrode was inserted through the chest wall for a distance of 1 to 2 cm., the deflections were as a rule slightly greater than those found in the corresponding overlying subcutaneous tissues (Fig. 7, *B1-9*). However, the configuration of the patterns obtained from corresponding points inside and outside the chest wall remained much alike in most regions. The chief exception to this rule was noted in the configuration of T waves in certain axillary positions. As electrodes were inserted from the lateral walls of the chest deeper into lung structure, approaching the posterior aspect of the heart, the deflections became considerably greater (Fig. 7, *C1-6*, *D1-6*). The patterns in superficial parts of the lung, which showed resemblance to those of the outer chest wall, were considerably different from those obtained in deeper parts of the lung near the heart. Tracings made at 1 cm. distances from each other showed these changes to be gradual in occurrence.

Discussion. In the dog and the rat there appears to be distribution of one pattern of potential variation to nearly all parts of the body below the diaphragm, including the surfaces of the intra-abdominal tissues. In the dog, fairly rapid decrement can be demonstrated on the diaphragm as distance from the heart increases. Slight decrement can also be demonstrated on the upper abdominal wall. In the human, as our experiments have shown, there is a much larger area of practically uniform distribution of potential on the lower part of the body than had hitherto been thought. The human differs from the dog in that, in the former, it is possible to demonstrate that precordial patterns of potential are distributed to some extent on the surface of the upper abdomen. However, limited studies of the potential of the interior of the stomach in the human fail to reveal evidence of distribution of the precordial patterns to that region. The pattern of potential variation conforms fairly closely to the diaphragmatic pattern, but tends to be of greater magnitude than those of the legs. Thus, in the human as well as in the dog, it may be that there is widespread distribution of the diaphragmatic pattern of potential on and below the diaphragm and that in parts of the body near the heart, the phenomenon of decrement may exist in the human as it does in the dog. It is probable that the distribution of the precordial patterns of potential to the upper abdomen in the human is mainly through electrical pathways in the abdominal wall.

It was known by Einthoven that the potential variation of cardiac origin of all parts of the surface of each extremity is practically uniform and that the potential is practically identical in both legs. We have previously shown that slight differences of potential can often be recorded when electrodes are paired on the outer and inner aspects of the upper arms near their attachments to the trunk, particularly on the left side.³ These changes, however, are not great enough to invalidate Einthoven's assumption regarding the distribution of potential in extremities, which is one of the minor supports of the equilateral triangle hypothesis. His major assumption, although he did not explicitly state it as such, is that the body tissues function as a homogeneous fluid volume conductor. If this assumption be valid, only relatively unimportant error would be introduced by his further assumptions that: (1) the heart may be considered as equidistant from the vertices of the angles of an equilateral triangle, formed by lines connecting the attachments of the arms and the pubis; and (2) the heart is far enough away from the extremities that no part has an advantage over any other part, by virtue of its position, in producing potential changes in the extremities.

On the basis of evidence now at hand, it seems safe to say that the laws governing the distribution of potential in an extensive medium of uniform conductivity are not applicable to the distribution of potential throughout the human body, probably because of differences in the electrical characteristics of the various tissue structures between the heart and the body surface. All of our findings seem to emphasize the importance of these structures even to the extent that the body can be divided into various regions, in each of which certain characteristic differences in the distribution of potential can be discovered. Thus, as has been shown, in the region closely surrounding the heart (probably not more than 2 or 3 inches from some part of its external surface) the potential variations appear to decrease very markedly as distance from the heart increases. Moreover, throughout this region, the pattern of potential variations is found to differ in positions near each other just as it does on the precordium (which is a part of the region under consideration).

The C_1 , extra-apical, and diaphragmatic patterns, however, each of which has its own region of distribution, appear to dominate the potential variations of nearly all other parts of the body. These patterns, as judged from the effects produced on them by myocardial infarction, seem almost independent of each other, although complete independence would doubtless be impossible. The modes by which each of the three is directed to its own large area of body surface, where the effect of other ventricular electrical activity is practically negligible, cannot be satisfactorily explained at this time. It seems possible that the distribution of these three patterns

depends largely on areas of contiguity of the diaphragm and the lungs to the heart and the special anatomic and electrical characteristics of these structures. However, studies in patients with unilateral pneumothorax in which the lung is not in contact with the chest wall (not reported in this paper) indicate that conduction may occur *via* the precordium and lateral chest wall independently of the lungs. Thus, it seems possible that the C_1 and extra-apical patterns receive some accretion *via* the precordium as well as through the lungs. If, as seems certain, precordial and diaphragmatic potential variations depend mainly on electrical activity in limited volumes of the heart, our demonstration of the distribution of these potential patterns indicates that electrical activity in certain limited volumes of the heart dominates the potential variations of large areas of the body surface, including the extremities.*

The phenomenon of decrement observed in the upper part of the body must depend on the structure and electrical characteristics of the conducting media. In the case of extensive conductors, the magnitude of potential change may be expected to vary in some inverse relationship with distance from the source of electrical activity. The practically uniform distribution of potential throughout all parts of the surface of any one of the arms or legs, irrespective of relative distances from the heart, is probably owing to the facts that: (1) the tissues of the arms and legs are good conductors; and (2) because of their structure further dispersion of electrical pathways is not possible, thus current flow throughout extremities is in effect limited to one dimension so that the extremities function electrically much as wires. The comparatively slight decrement in the diaphragmatic pattern of potential on the trunk below the diaphragm is more difficult to explain, although after this pattern has been distributed throughout the diaphragm, which probably functions as a plane conductor, the situation may be somewhat analogous to that of the extremities. The apparently limited distribution of the diaphragmatic pattern above the diaphragm is a perplexing phenomenon and raises the question as to what part the lungs play in obstructing the upward distribution of this pattern. That it is well distributed just above the diaphragm is clearly shown when the exploring electrode is punctured through the diaphragm of the dog.

The demonstration, by the use of the method of balanced potentials, of hitherto unsuspected facts regarding the distribution of potential suggests that certain changes in the methods of electrocardiography may be desirable. One of the first questions we must ask ourselves is, whether the preoccupation with limb leads is justifiable. If the equilateral triangle hypothesis cannot be upheld,

* We do not imply by these statements that electrical activity in any part of the heart fails to influence the potential of any part of the body. We are concerned here with those effects which dominate the pattern.

limb leads must justify themselves entirely on empirical grounds. The following statements may be made in defense of them: (1) limbs are convenient positions for the application of electrodes, (2) countless limb lead electrocardiograms have been made, (3) limb leads have proven themselves satisfactory for the study of abnormal cardiac mechanisms, and (4) limb leads may demonstrate abnormality on the posterior wall of the left ventricle, whereas chest leads usually fail to do so.

We have already described how Lead I is formed.² Lead II is formed by the diaphragmatic pattern of potential, minus the C_1 pattern after each has undergone the decrement found in the positions to which the electrodes are attached. Lead III is formed by the diaphragmatic type of potential, minus the extra-apical pattern after each has undergone decrement. The measurements of the differences between pairs of these three types of potential variation, each of which is derived mainly from separate parts of the heart and each of which is greatly modified, depending on the characteristics of the electrical pathways between the heart and the limbs, have led to endless difficulties in standardization, questions as to the meaning of the direction and amplitude of various deflections, of slurrings and notchings. It would seem to us far more desirable to measure the potential of each of these areas against a constant potential if this were possible. The method of balanced potentials has already been shown, by experimental check, to be a step in the direction of this objective, but it is too time-consuming for routine clinical electrocardiography. However, as we have shown, the right scapular region is an area where ventricular potential is most often nearly the same as that of balanced potentials. Consequently the results obtained by pairing an electrode on this area with the exploring electrode are in most cases almost identical with those obtained by the method of balanced potentials. Even in cases with marked potential variations on the body surface, such as may be found in ventricular hypertrophy, the differences are not likely to be great. It seems to us, therefore, that a closer approximation to the potential of the exploring electrode can be recorded by this procedure than by any other simple method.

After fairly extensive clinical study we are convinced that a series of leads made with the exploring electrode on positions C_1 to C_6 inclusive and on either the right or left leg, paired with an electrode on the right scapular region, reflects more information of clinical value than can be obtained by conventional methods of pairing electrodes. In our opinion all three limb leads could be discarded without sacrificing any real values, and with the very great advantage of ridding ourselves, once and for all, of the infinite variability of pattern found in these leads. Much of this variability is dependent on the electrical characteristics of tissues outside the heart, so that it is of dubious clinical significance.

The matter may be illustrated by discussion of "posterior" infarction. This is the location of injury which, above all others, has justified the use of limb leads because of the changes produced in Leads II and III. However, these changes are nearly all owing to change in the diaphragmatic pattern of potential. Lead II is more dependable than Lead III for the diagnosis of posterior infarction, because potential variation in the right arm is usually considerably less than in the left arm, so that the changes in the diaphragmatic pattern are less obscured in Lead II. The superiority of a lead in which an electrode is placed over the right scapula instead of the right arm is owing to the fact that potential variations are even less on the scapula than on the arm, so that a closer approximation to the really significant changes in the diaphragmatic pattern is obtained.

In view of the inadequacy, suggested by this study, of the generally accepted methods of making electrocardiograms, one may ask how methods which seem to be so imperfect and to include so much irrelevancy have enabled electrocardiography to maintain its important position in cardiac diagnosis. So long as limb leads only were being made, electrocardiography owed much of its standing to the fact that it was almost always a satisfactory procedure for the display of abnormalities of cardiac mechanism. That it had obvious limitations as a diagnostic procedure for the discovery of injury of the myocardium was not difficult to demonstrate. That these limitations were not even greater is because (1) the potential variations of ventricular origin on the right arm are as a rule comparatively small in magnitude, and (2) they are relatively little affected by involvement of the left ventricle. Thus, Leads I and II usually bear some resemblance to the extra-apical and diaphragmatic patterns of potential variation respectively, whether these be normal or abnormal in contour. Since the introduction of chest leads, the latter have been generally regarded as a useful supplement to the supposedly fundamentally important limb leads, based on the fact that in certain cases the chest leads alone reflect evidence of myocardial injury. Even the potential variations of the most inappropriate positions that can be chosen for the electrode paired with the exploring chest electrodes are as a rule unable to obscure the value of chest leads, because of the fact that potential variations at positions so near the heart as the anterior chest wall tend to be much greater in magnitude than those of positions farther from the heart. It is evident that not all of the various methods heretofore proposed for pairing with the exploring chest electrode could yield the most significant tracings obtainable and there is no clear evidence that any of them achieve this goal. On the basis of the data presented in this paper it appears possible to devise simple electrocardiographic methods which may clarify the significance of recorded deflections and facilitate the satisfactory standardization of electrocardiographic leads.

Explanation of Figures 2, 3, 4, 6, and 7. FIGURE 2. Series *A* and *B* were obtained from a patient with right bundle branch block, the method of balanced potentials being used. *A1* represents the potential variations of the C_5 position and *A2* the potential variations of the left arm. *A3* was made in the same way as *A1* except that the sensitivity of the galvanometer was reduced so that the deflections would be comparable with those obtained when the exploring electrode was on the left arm. *B1* was made with the exploring electrode on the C_1 position and *B2* with the exploring electrode on the right arm. *B3* was made in the same way as *B1* except for reduction in the sensitivity of the galvanometer.

In series *C* and *D* the exploring electrode was paired with an electrode placed over the spine of the right scapula. *C1* represents the potential variations of the C_5 chest position. *C2* represents the potential variations of the left arm. *C3* (recorded simultaneously with *C2*) was made in the same way as *C1* (with the exploring electrode on the C_5 chest position) except that the sensitivity of the galvanometer was reduced. *D1* represents the potential variations of the C_1 chest position in a patient with left bundle branch block. *D2* represents the potential variations of the right arm. *D3* recorded simultaneously with *D2* was made in the same way as *D1* except that the sensitivity of the galvanometer was reduced. The second beat in *D2* and *D3* is a ventricular extrasystole. These illustrations are presented to show the resemblance between the C_1 and right arm patterns and the C_5 and left arm patterns of ventricular potential variations, when the differences due to decrement as distance from the heart increases are neutralized by appropriate adjustment in the sensitivity of the galvanometer.

Series *E* represents electrocardiograms made by the method of balanced potentials with the exploring electrode on various positions of the right upper part of the body. *E1* represents the potential variations of the C_1 position. *E6* was obtained with the exploring electrode on the right anterior axillary fold. *E2-5* were obtained from positions 1 to $1\frac{1}{2}$ inches further from the C_1 position respectively along the line between the C_1 position and the right anterior axillary fold. *E7* represents the potential variations of the right arm and *E8* those of the tip of the right shoulder, *E9* and *E10* were made with the exploring electrode in positions along the line between the tip of the right shoulder and the spine of the right scapula. In *E11* the exploring electrode was over the spine of the right scapula and in *E12* it was placed below that position. This series of tracings illustrates the similarity of ventricular potential variations over a large part of the right thorax, shoulder and arm. Decrement as distance from the heart increases is demonstrated.

Series *F* represents electrocardiograms made by the method of balanced potentials in a patient with left ventricular hypertrophy, the exploring electrode having been placed on various positions of the left upper part of the body. *F1* was made along a line between a surface point just outside the cardiac apex and the tip of the left shoulder, the exploring electrode having been placed at a level $1\frac{1}{2}$ inches above the cardiac apex. The tracing made from a position just outside the apex was practically identical with *F1*, there being no appreciable decrement. *F4* represents the potential variations of the left anterior axillary fold and *F2* and *F3* those of intermediate positions between *F1* and *F4*. *F5* represents the potential variations of the left arm and *F6* those of the tip of the left shoulder. *F9* represents the potential variations over the spine of the left scapula; *F7* and *F8* those of intermediate positions between the tip of the left shoulder and the spine of the left scapula. This series illustrates the similarity of ventricular potential variations over a large part of the left side of the thorax, shoulder and arm. Decrement as distance from the heart increases is demonstrated.

Series *G* (same patient as in series *E*) made by the method of balanced potentials with the exploring electrode on various positions below the umbilicus. In *G1* the exploring electrode was on the left leg, in *G2*, on the right flank, in *G3* below the C_1 position, in *G4* below the C_3 position, in *G5* below the C_5 position, in *G6* on the left flank, in *G7* on the left lower back and in *G8* on the right lower back.

This series is marked by uniformity of the patterns with only very slight decrement as distance from the heart increases.

Series *H* (same patient as series *E*) made by the method of balanced potentials. *H1* was made with the exploring electrode on the right side of the back at the level of the diaphragm. Note the similarity of pattern to the *G* series. *H2* and *H3* were made along a vertical line erected from the *H1* position, at 2-inch intervals. Note the rapid decrement above the diaphragm. Continuance of exploration upward (not shown here) reveals change to the pattern shown in *E12*, i. e., from the diaphragmatic to the C_1 pattern.

Series *J* (same patient as in series *E*) made by the method of balanced potentials. *J1* was made with the exploring electrode on the left side of the back at the level of the diaphragm. Note the similarity of pattern to the *G* series and that of *H1*. *J2* and *J3* were made at 2-inch intervals along the vertical line erected from the *J1* position. Note the rapid decrement above the diaphragm. This demonstration can be made because potential variation at the C_5 position was slight and there was consequently insignificant potential variation of the C_5 type on the left side of the back.

The *K* series (made by pairing the exploring electrode with one placed over the spine of the right scapula) is designed to illustrate the abrupt change in pattern of potential variation on the left side of the back at about the level of the diaphragm due to the distribution of both the diaphragmatic and extra-apical patterns of potential into this area. In *K1* the exploring electrode was placed on the left leg. In *K2* it was placed on the left side of the back 4 inches below the level of the attachment of the left diaphragm. *K3* was made from a position $1\frac{1}{2}$ inches higher, *K4* from a position just below the diaphragm, *K5* from a position just above the diaphragm, and *K6* with the exploring electrode on the C_6 position. As the exploring electrode is moved upward the increasing influence of the extra-apical pattern is readily discerned.

(Camera speed in the *F* and *K* series was 41 mm. per second. In all others it was 75 mm. per second.)

FIGURE 3. In the *A* series the exploring electrode (whose location on the chest at various C positions is designated) was paired with an electrode on the right scapula. The QRS complex begins at approximately the same instant in all tracings. The upward deflection increases in amplitude with each change in position toward the left as far as the C_4 position. Frequently in the case of normal hearts it continues to increase to the C_5 position. At positions C_4 , C_5 and C_6 an initial small downward deflection is often present as in this case and is normal with this method of pairing or when the method of balanced potentials is used. When the initial downward deflection is present there is delay in the onset of the upward deflection. The major deflections at C_5 and C_6 positions become progressively smaller than those obtained from the C_4 position in this case, because the heart was rather small so that decrement begins to manifest itself as distance from the heart increases.

In the *B* series, *B1* is the CR_1 lead obtained from a patient with old myocardial infarction and *B5* is the CR_5 lead. *B2*, *B3* and *B4* are tracings obtained from three intermediate positions successively farther to the left. Note the gradual transition from the CR_1 to the CR_5 pattern.

The *D* series is made by pairing the exploring electrode with one on the

right scapula as in the *A* series. The small upward and deep downward deflections noted at the C_1 , C_2 and C_3 positions are completely lost at C_4 and replaced by a small rounded upward deflection. The notching is caused by a second pair of upward and downward deflections whose time incidence falls considerably later. These latter waves become much more prominent at the C_5 and C_6 positions.

FIGURE 4. The tracings were all obtained from a patient with an intraventricular conduction defect.

In the *A* series the exploring chest electrode was paired with an electrode on the right scapula. In each instance the position of the exploring chest electrode is indicated by the appropriate *C* designation. The QRS complex begins at approximately the same instant in each position. In the tracing made at the C_4 position there is definite notching. The first pair of upward and downward deflections corresponds in time to those found at the C_1 , C_2 and C_3 positions. The second pair is represented at positions further to the right on the chest as slight slurring on the upstroke of the terminal major upward deflection. In positions further to the left, however, this second pair of deflections becomes larger. (Film speed 75 mm. per second.)

The *B* series was obtained by pairing electrodes on the abdomen, the left arm electrode being placed on a vertical line below a *C* position and the right arm electrode placed on a continuation of this vertical line just below the umbilicus. In *B1* the vertical line was extended from the C_1 position, in *B2* from the C_2 position, etc. Note the similarity of ventricular patterns, except for size of deflections, in *B1*, *B2*, *B3* and *B6* to those obtained when the exploring electrode was on the C_1 , C_2 , C_3 and C_6 chest positions respectively. The *B3*, *B4*, *B5* and *B6* patterns show evidence of being influenced not only by the *C* pattern directly above each but by adjacent *C* patterns as well. These effects are seen most clearly in *B3* which shows the notch found in the QRS complex of the C_4 tracing, and in *B6* which shows some of the early downward deflection found in the QRS complex of the C_5 tracing. (Film speed 41 mm. per second.)

The *D* series was made by pairing an exploring electrode on the upper abdomen with an electrode on the right scapula. In each instance the *D* position was directly below the corresponding *C* chest position and just below the costal margin. The similarity of pattern in each instance to that of the *C* position just above is obvious.

In the *E* series the exploring electrode was placed 2 inches below the corresponding *D* position. Decrement is quite obvious although in *E5* and *E6* considerable change in pattern occurs so that there is no longer any resemblance to the C_5 and C_6 patterns. (Film speed 41 mm. per second.)

FIGURE 6. All tracings made on one dog. (Film speed 75 mm. per second.) The exploring electrode in each instance was paired with an electrode inserted into the subcutaneous tissues of the right foreleg. The polarity is such that an upward deflection represents relative positivity of the exploring electrode.

In the *A* series the positions of the exploring electrode were as follows: *A1* subcutaneous tissue of right leg, *A2* left leg, *A3* lower abdomen, *A4* upper abdomen, *A5* high as possible in the subcostal angle, *A6* within lower part of the abdominal cavity, *A7* within upper part of the abdominal cavity, *A8* within abdominal cavity high as possible in subcostal angle. Note the similarity in pattern of all these tracings and the fact that those obtained from the subcostal angle and from within the upper abdomen show larger deflections than those obtained when the exploring electrode was farther from the heart.

In the *B* series the abdomen was open and the exploring electrode placed on the undersurface of the diaphragm. In *B1* it was placed on the right lateral margin, in *B2*, 1 inch toward the midline, in *B3* just to the right of the

midline, in *B4* directly under the heart, in *B5* just to the left of the heart, in *B6* 1 inch from the left lateral margin, in *B7* on the left lateral margin. Note the similarity of patterns in *B1*, *B2*, *B6* and *B7* to the *A* series (except for absence of the small initial downward deflection in positions on the right side of the diaphragm), the differences in T waves in positions near the heart and the increase in size of QRS deflections as the heart is approached.

In the *C* series the exploring electrode was punctured through the dome of the left diaphragm. In *C1* it was placed just above the diaphragm and in *C2*, *C3*, *C4* and *C5* it was moved successively 1 cm. higher into the lung substance. Note the general resemblance of the QRS complex in *C1* and *C2* to those of *B5*, *B6* and *B7*. The T waves in *C1* and *C2* are not very different from those of *B6* and *B7* although the pattern changes as the electrode is inserted further into the lung substance.

In the *D* series, the exploring electrode was punctured through the dome of the right diaphragm. In *D1* the electrode was placed just above the diaphragm and in *D2*, *D3* and *D4* it was moved successively 1 cm. higher into the lung substance. The QRS complex in *D1* is very similar to that of *B1*, *B2* and *B3* (except for absence of the small terminal upward deflection in *D1*), although the T wave is comparatively greater in amplitude. Note the changes in pattern as the electrode is inserted higher into the lung substance.

FIGURE 7. All tracings made on the same dog as in Figure 5. (Film speed, polarity and position of the electrode paired with the exploring electrode are all the same as in Figure 5.)

In the *A* series all tracings were made with the exploring electrode placed along a horizontal line on the thorax at the level of the heart. In *A1* the exploring electrode was placed far to the right of the precordium at the right posterior axillary line. The anterior midline was approached in successive steps in *A2*, *A3* and *A4*. *A5* was made with the exploring electrode on the midline and *A6* directly over the body of the heart. *A7*, *A8* and *A9* positions were successively further to the left, the last being along the left posterior axillary line. Note the close similarity of pattern in positions *A3* to *A7* inclusive and the fact that the more nearly the exploring electrode was placed to the heart, the larger the deflections. The dog seems to differ from the human in that normally it does not tend to show a constantly changing pattern of potential variations in the precordial region, although decrement is conspicuous as distance from the heart increases.

In the *B* series the exploring electrode was punctured through the chest wall at positions corresponding to those of the *A* series. There is marked similarity in the QRS complex in each *B* tracing to the QRS complex of the overlying *A* position, except that in the case of positions comparatively near the heart (*B3* to *B7* inclusive) the deflections obtained just inside the chest wall are considerably larger than those obtained just outside. The reasons for the differences in T waves in *A2* and *B2* and *A8* and *B8* positions are not clear.

The *C* series. In *C1* the exploring electrode was inserted into the subcutaneous tissue of the right lateral wall of the chest slightly anterior to the position in *A2*. In *C2* the electrode was punctured into the right lung in the direction of the heart for a distance of approximately 2 cm. In *C3*, *C4*, *C5* and *C6* the electrode was moved successively 1 cm. in the direction of the heart. Note the gradual change in pattern and increase in size of deflections as the heart is approached.

The *D* series. In *D1* the exploring electrode was inserted into the subcutaneous tissue of the left postero-lateral wall of the chest, slightly posterior to the position in *B2*. In *D2*, *D3*, *D4*, *D5* and *D6* the electrode was punctured through the chest wall into the left lung and moved successively nearer the heart as in the *C* series. Note the changes in pattern and increase in size of deflections as the heart is approached.

Summary. 1. Patterns of potential variation found in regions not more than 2 or 3 inches from some part of the external surface of the heart differ from each other appreciably at positions no more than 1 cm. from one another. Furthermore, in these regions the magnitude of potential variations decreases rapidly as distance from the heart increases.

2. The pattern of potential variation found at the C_1 position can be demonstrated in various directions on the body surface to the right of the C_1 position with decrement as distance from the heart increases. On an area as far from the heart as that overlying the spine of the right scapula, decrement is so great that the potential variations are usually of negligible magnitude. When an electrode placed on this area is paired with an exploring electrode, the results are usually not significantly different from those obtained by the use of the method of balanced potentials.

3. The pattern of potential variation found on the surface of the chest slightly to the left of the cardiac apex (somewhere between the C_4 and C_6 positions, depending on the relation of the apex to the chest wall) can be demonstrated in various directions on the surface to the left of that position, with decrement as distance from the heart increases.

4. Not only do we know that the C_1 and extra-apical patterns are distributed on the surface of the anterior abdominal wall with very rapid decrement as distance from the heart increases, but evidence is here reported that the patterns found on the precordium between these two positions are also distributed on the anterior abdominal wall with rapid decrement as distance from the heart increases.

5. Aside from the precordial patterns mentioned above, the only other that we have found distributed on the body surface is one which we have called "the diaphragmatic pattern." The distribution of this pattern above the diaphragm with rapid decrement as distance upward increases can be demonstrated on the back. It may also be distributed above the diaphragm anteriorly but we have not been able to demonstrate it here, probably because of the magnitude of the precordial potentials in such regions. It seems to be distributed everywhere below the diaphragm with but little decrement on the body surface as distance from the heart increases. It can also be demonstrated in the lower part of the esophagus and the stomach, although in these areas the potential variations are greater in magnitude than on the surface.

6. Studies on experimental animals indicate that the diaphragmatic pattern of potential can be found everywhere below the diaphragm and on all parts of the under and upper surfaces of the diaphragm except in areas very near the heart. Decrement on the diaphragm and within the upper part of the abdomen as distance from the heart increases is demonstrable.

7. The distribution of the various potential patterns which seem to be directed to certain areas and partially insulated from other areas must depend on the special electrical characteristics and anatomic structure of the various tissues by which contact with the heart is maintained and through which electrical pathways to the body surfaces function.

8. If, as our studies seem to indicate, the patterns of potential variation found on limbs are each derived mainly from separate parts of the heart, and are subject to modification depending on the electrical and anatomic characteristics of the tissues which form the electrical pathways between the epicardium and the extremities, limb leads do not merit the scientific standing that they have been supposed to possess, and there seems to be little reason to continue making them.

Conclusion. Much of the confusion which now exists in clinical electrocardiography could be eliminated if in all leads one of the paired electrodes were attached to an area of relatively slight potential variation such as the right scapular region. Under such circumstances an electrocardiogram may be obtained which presents a relatively undistorted record of the potential variations of the exploring electrode. From data now available it is possible to say that the exploring electrode should be placed on a number of chest positions such as C_1 to C_6 inclusive, if one wishes to acquaint himself with the chief features of the various patterns which may be formed on the surface of the chest, including the two widely distributed to the upper parts of the trunk and arms. In order to obtain information regarding the pattern widely distributed below the diaphragm, it is necessary to place the exploring electrode on some position at least a few inches below the parietal attachments of the diaphragm. The best position or set of positions for this purpose has not as yet been determined.

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TREATMENT OF LEG ULCERS WITH BLOOD AND CONCENTRATED PLASMA

BY MEYER NAIDE, M.D.

INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

(From the Peripheral Vascular Section of the Edward B. Robinette Foundation,
Hospital of the University of Pennsylvania)

LEG ulcers in patients with peripheral vascular disease are notoriously difficult to heal, and in some cases incurable. Many methods

and drugs are used in the treatment of such ulcers. These include sulfonamides locally, various antiseptics, stimulants (such as cod-liver oil ointments), gelatin boots, mecholyl iontophoresis, and so on.

Since ischemic ulcers could not be supplied with sufficient blood through occluded arteries, the idea suggested itself of withdrawing blood from the patient's antecubital vein and applying it directly to the surface of the ulcer. The method adopted, in October 1941, consisted simply in dropping or spraying the blood on the ulcer and allowing it to clot. With this simple method, obtaining the curative agent from the patient himself, ischemic ulcers were healed which had failed to heal by other methods. Then the same method was applied to varicose ulcers and these healed even more rapidly, a number after only one application of blood. Relief of pain and subsidence of reaction in the tissue around the ulcer followed the first or second application in most patients.

When it was found that blood could heal chronic ulcers, concentrated plasma made from dried plasma was tried. This supplied 8 times the quantity of constituents of an equal volume of whole blood, with the exception of red and white cells. The concentrated plasma has proved to be more effective than whole blood.

Method. The ulcer is cleaned gently with hydrogen peroxide and mopped with sterile gauze. One to 5 cc. of blood are drawn into a sterile syringe from the patient's antecubital vein. The blood is then applied to the surface of the ulcer simply by placing a number of drops on it sufficient to cover the lesion. The drops of blood may be smeared or spread over the surface of the ulcer so that a film of blood of any desired thickness may be obtained. One cc. of blood will cover an area of approximately 30 sq. cm. or 5 sq. in., so that only a small quantity of blood is required. The blood is then permitted to clot. The patient holds his leg in a position which prevents the blood from running off the ulcer. The clotting time is shortened considerably by having air blown on it by a fan. The clotting (solid) time in still air has ranged from $\frac{1}{2}$ to 2 hours. A fan shortens this time to 15 minutes to 1 hour. After the blood has clotted solidly a sterile dressing is applied to the treated ulcer. The lesion is reexamined within 1 to 3 days and if the clot has been broken up or liquefied the entire procedure is repeated. For complete healing to take place, 1 to 20 applications of blood may be necessary. The larger the lesion the greater the number of applications. Most of the patients were ambulatory but patients are asked to rest as much as possible during the course of treatment. A modification of the method was used on some patients with large lesions. Five cc. of the patient's blood were placed in an ordinary sterile nose and throat atomizer. The surface of the ulcer was then sprayed with the blood and the blood allowed to clot in the manner described above.

To treat ulcers with concentrated plasma we have used dried plasma, diluted with only one-quarter the amount of distilled water which would ordinarily be used to restore it to the normal concentration of human plasma. In this manner the plasma contained 8 times the clotting elements and all other substances, minus red and white cells, present in an equal volume of whole blood. The concentrated plasma is then applied to the ulcer in exactly the same manner as is whole blood. The plasma is quickly clotted

by fanning or more slowly clotted without the use of a fan. Although the plasma contains sodium citrate this does not prevent it from clotting on the surface of an ulcer. The sterile ampoule vial of concentrated plasma can then be left in a refrigerator and used as needed.

*A**B*

FIG. 1.—Ischemic ulcer in a patient with diabetes mellitus. Duration of ulcer 13 months. *A*, Before treatment; *B*, 8 weeks later. Completely healed after 17 applications of patient's blood.

Results. Fifteen patients with leg ulcers have been treated with the local application of blood by the methods described above. Ten of the ulcers were on an ischemic basis, caused by arteriosclerosis and thromboangiitis obliterans; 5 were varicose ulcers. The duration of the ulcers was from 1 month to 3½ years. All of them had been treated by various methods without healing or improving. The ulcers varied in size from 1 to 7 cm. in diameter. Nine of the 10 patients with ischemic ulcers had extreme grades of arterial occlusive disease, having either popliteal or femoral thrombosis with little or no capacity for vasodilatation. One to 20 applications were required to heal the ulcers.

Five of the ischemic ulcers were healed with blood; 1 is almost completely closed and 4 failed to heal.

Four of the 5 varicose ulcers were healed. The fifth varicose ulcer is almost healed.

Eight of the 9 ulcers which healed have remained healed for 1 to 18 months. One ulcer broke down after having been healed for 4 months.

The crust that formed on a healed ulcer gradually fell off after epithelization had taken place under it. Pain was a prominent symptom in all these patients and its rapid relief by 1 or 2 applications of blood was a striking feature of the treatment. Even those ulcers which could not be healed were painless or less painful during the course of therapy. All the patients were eager to return for further applications of blood until the ulcer healed or until we decided that the ulcer could not be healed by this method.

Another result of the treatment was the rapid reduction of the inflammatory reaction in the skin surrounding the varicose ulcers. An angry, purplish looking skin would begin to look more healthy following the first or second application of blood. The ulcers themselves rapidly became red, normal granulating tissue replacing grayish, sloughing surfaces. Three patients on whom we applied concentrated plasma had received previous treatment with whole blood. These patients improved more rapidly with the plasma than with the whole blood.

We have found the method to be harmless. Accumulation of pus occurred under a crust in 2 patients. This was readily drained by lifting off the crust after softening it with petrolatum for 24 hours. The presence of pus under a crust should be suspected if pain is not relieved.

A blood Wassermann test was done in 10 patients and found to be negative. Concentrated plasma instead of the patient's blood can be used in those with a positive blood Wassermann.

Discussion. Although we were able with blood to relieve pain quickly, reduce the inflammatory reaction and heal 9 of 15 chronic ulcers that had resisted previous methods of treatment, the mechanism of action is unknown. We know of no way of telling whether the

ulcers heal because required elements of nutrition are being supplied or because the ulcers are sealed mechanically, which permits healing to take place under the crust. The rapid relief of pain, with blood, which did not occur when other local treatment was used, suggests that the blood functioned as more than a mere mechanical seal. An interesting observation was made when concentrated plasma was used. Within 5 minutes after the plasma is applied the surface of the ulcer can be seen to change from a dull grayish pink to a bright red color, indicative of increased blood flow, at least temporarily. Perhaps the concentrated plasma with a high osmotic pressure causes capillary dilatation and increased blood flow at the surface of the ulcer.

Various substances such as dyes and tannic acid have been used to produce a crust or eschar on lesions, chiefly on burns. Blood and plasma have never been used for local medication as far as I know. This method may prove of value in the delayed healing of other wounds in which impoverished nutrition may play a part.

Summary. A simple method has been described for the treatment of ischemic and varicose leg ulcers with the patient's own blood and with concentrated plasma. Nine of 15 ulcers, refractory to other treatment, were healed, 2 were improved and 4 failed to heal. This treatment results in rapid relief of pain and subsidence of the local inflammatory reaction.

A STUDY OF THE SPLENIC VENOUS BLOOD

WITH PARTICULAR REFERENCE TO THE HEMATOCRIT PERCENTAGE
AND THE HEMOGLOBIN CONCENTRATION OF THE ERYTHRO-
CYTES, BEFORE AND AFTER SPLENIC ARTERIAL INJECTION OF
ADRENALIN*

BY CECIL JAMES WATSON, M.D., PH.D.

PROFESSOR OF MEDICINE, UNIVERSITY OF MINNESOTA HOSPITAL

AND

JOHN RANDOLPH PAINE, M.D., PH.D.

ASSOCIATE PROFESSOR OF SURGERY, UNIVERSITY OF MINNESOTA HOSPITAL
MINNEAPOLIS, MINN.

(From the Departments of Medicine and Surgery, University of Minnesota Hospital)

OUR interest in the blood of the splenic vein was aroused after we had repeatedly observed the effect of subcutaneous adrenalin in producing outspoken increases in the number of circulating erythrocytes.²⁰ These increases were usually associated with an obvious shrinking of the enlarged spleen. Many similar observations are recorded in the literature but relatively little has been written

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about the red blood cells coming from the spleen under these conditions. A complete review of the subject of splenic arteriovenous differences up to 1933 may be found in Lauda's excellent monograph on the physiology of the spleen.¹² The evidence collected by Lauda indicated that splenic contraction was an important factor in the transient erythrocytosis produced by adrenalin. The collected evidence also indicated that the erythrocytes in the splenic vein are less resistant to hypotonic saline than those in the artery, although Lauda himself was unable to obtain decisive data on this point. Subsequent studies by Heilmeyer¹⁰ and by Bergenheim and Fåhræus³ support the belief that the splenic vein erythrocytes are more spheroidal.

Our primary purpose in the present study was to determine the concentration of erythrocytes in the splenic vein before and after administration of adrenalin; since if the marked increases in circulating erythrocytes were due to contraction of the spleen and emptying of the splenic reservoir, then it was to be expected that the splenic vein blood would exhibit outspoken increases in hematocrit percentage and erythrocyte count.

Method. Studies have been carried out at the time of splenectomy in 9 cases. In each instance oxalated samples of blood were obtained from the splenic artery and vein, after which 4 to 6 minims of a 1:1000 adrenalin solution were injected into the splenic artery. Two to 6 minutes later samples of blood were again obtained, in each instance from the splenic vein, and in some instances from the artery as well. Insofar as possible, these samples were taken at the time of maximum splenic contraction, whenever this was observed. It may be noted that splenic contraction was often marked, especially in the larger spleens, while it was negligible in the cases of thrombocytopenic purpura. The contraction was at times of sufficient magnitude to enhance the delivery of a large spleen through the wound.

It is quite possible that more information might have been gained had it been feasible to obtain fractional blood samples from the splenic vein from the time of injection of adrenalin until well after its effect had passed. Cruikshank,⁵ for example, has reported that after section of the nerves to the cat's spleen, the first cubic centimeter of blood obtained from the splenic vein showed no change in red cell concentration while the 2d, 3d, and 4th cc., obtained individually, were increasingly concentrated, the 3d and 4th cc. exhibiting increases of 50% to 100% over the first. Although we have not obtained fractional samples in the present studies, we believe that much of the data obtained and shown in the accompanying tables are of decisive significance. The expected increase in hematocrit percentage and erythrocyte count in the splenic vein after adrenalin was noted in the majority of cases. Unexpectedly, the hemoglobin concentration of the red cells of these samples was commonly reduced, in some instances to a marked degree. (See Tables 1 to 9.)

In each instance the hemoglobin content of the blood samples was determined by means of the Evelyn photoelectric colorimeter.⁸ The hematocrit percentage (corrected for the oxalate), the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration were determined by Wintrobe's method.²¹ Resistance to hypotonic saline was determined by Meulengracht's method.¹⁶

Results

TABLE 1.—CASE 1. FAMILIAL HEMOLYTIC JAUNDICE, W. G., ♂, 44.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	12.0	36.4	3.80	95.8	31.6	33.9	0.68	0.50
Splenic artery	12.2	37.9	3.92	97.0	31.2	32.2	0.66	0.48
Splenic vein after adrenalin	14.0	53.1	5.46	97.5	25.8	26.5	0.70	0.62
Splenic artery after adrenalin	12.9	36.1	3.97	91.0	32.5	35.7	0.68	0.52

Spleen weight 1830 gm.

Microscopic: Marked pulp congestion with narrow sinuses.

TABLE 2.—CASE 2. FAMILIAL HEMOLYTIC JAUNDICE, A. S., ♂, 41.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	15.0	41.01*	4.26	96.2	35.0	36.6	0.62	0.46
Splenic artery	15.2	49.96*	5.00	99.5	30.4	30.6		
Splenic vein after adrenalin	17.5	61.20	6.40	95.5	27.3	28.6	0.68	0.54
Splenic artery after adrenalin	15.8	40.60	4.20	96.7	37.6	38.9	0.66	0.48

Spleen weight 675 gm.

Microscopic: Marked pulp congestion; sinuses prominent and open.

* This isolated discrepancy is unexplained except as an inadvertent exchange of the data for vein and artery, in which event the hematocrit percentage of 49.96 would be readily explained as due to a spontaneous partial emptying of the splenic reservoir.²⁰

TABLE 3.—CASE 3. FAMILIAL HEMOLYTIC JAUNDICE, J. B., ♀, 10.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic artery	13.65	39.3	4.33	91.0	32.0	35.3		
Splenic vein	14.50	40.6	5.01	81.0	29.0	35.7		
Splenic vein after adrenalin	14.80	46.1	5.43	85.0	27.2	32.1		

Spleen weight 240 gm.

Microscopic: Marked pulp congestion; sinuses mostly compressed; quite a few open and empty.

TABLE 4.—CASE 4. ACQUIRED HEMOLYTIC ANEMIA, O. H., ♀, 55

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	12.8	43.2	4.50	96.0	28.5	29.6	0.52	0.40
Splenic artery	13.0	40.2	4.10	98.1	31.7	32.4	0.50	0.40
Splenic vein after adrenalin	15.0	69.3	7.20	96.3	20.8	21.6	0.54	0.44
Splenic artery after adrenalin	13.8	45.4	4.95	91.7	27.9	30.4	0.52	0.40

Spleen weight 420 gm.

Microscopic: Little or no congestion. Sinuses prominent, containing moderate numbers of erythrocytes, and in many areas large numbers of round cells having the appearance of desquamated sinus endothelial cells. The walls of the sinuses in these areas are denuded. No myeloid metaplasia. Marked hemosiderosis.

TABLE 5.—CASE 5. CIRRHOSIS AND CONGESTIVE SPLENOMEGALY, I. A., ♀, 50.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill. per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	11.1	33.10	3 61	91.7	30.8	33.5	0.46	0.38
Splenic artery	11 0	33.30	3 60	92.5	30.6	33 1	0.46	0.36
Splenic vein after adrenalin	13 2	59.79	6 10	98 0	21 7	22 1	0.50	0.40
Splenic artery after adrenalin	11 5	38 60	4 00	96 5	28 8	29 8	0.46	0.38

Spleen weight 865 gm.

Microscopic: No evident congestion. Sinuses open and prominent. Diffuse reticular hyperplasia and early fibrosis.

TABLE 6.—CASE 6. CHRONIC MYELOID LEUKEMIA WITH ASSOCIATED MILD HEMOLYTIC ANEMIA, E. V., ♀, 55.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill. per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	12 2	42 33	4 10	103	29 7	28 8	0.46	0.38
Splenic artery	12 3	42 38	4 18	101	29 4	29 0	0.46	0.36
Splenic vein after adrenalin	14 8	65 32	6 81	96	21 7	22 7	0.48	0.40
Splenic artery after adrenalin	12 5	41 39	4 02	103	31 1	30 2	0.46	0.38

Spleen weight 1390 gm.

Microscopic: Diffuse myeloid metaplasia with numerous megakaryocytes. Considerable pulp congestion. Sinuses compressed.

TABLE 7.—CASE 7. THROMBOCYTOPENIC PURPURA, M. D., ♀, 24.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill. per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	13 9	43 6	4 20	103 8	33 1	32 1	0.46	0.40
Splenic artery	13 6	37 0	4.06	91 1	31 0	36 6	0.44	0.34
Splenic vein after adrenalin	13 5	43 6	4.45	98 0	30 3	31 1	0.48	0.40
Splenic artery after adrenalin	13 5	41 4	4.10	101 0	33 0	32.6	0.46	0.40

Spleen weight 235 gm.

Microscopic: Normal.

TABLE 8.—CASE 8. THROMBOCYTOPENIC PURPURA, E. R., ♀, 14.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill. per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility	
							H ₁	H ₂
Splenic vein	12.15	37 0	4 31	85 8	28 2	32 8		
Splenic artery	13.15	39 0	4 34	90 0	30 3	33 7		
Splenic vein after adrenalin	10 67	38 0	3 84	100 0	27 7	28 0		

Spleen weight 152 gm.

Microscopic: Normal.

The data shown in the tables reveal: (1) the marked increase in concentration of red blood cells in the splenic vein blood after injection of adrenalin into the splenic artery in the majority of cases studied; (2) the reduced hemoglobin concentration of the red cells (MCC) under these circumstances. There is little doubt that the

hemoconcentration noted in the splenic vein blood after adrenalin is due to contraction of the spleen and at least partial emptying of the splenic reservoir. The conclusion is inescapable that the necessary preliminary to this phenomenon is a partial separation within the spleen of red cells and plasma, quite in accord with the observations of Knisely¹¹ and Fåhræus.⁹ Whether the circulation is closed⁹ or open¹⁵ would appear to be entirely immaterial insofar as a partial separation of red cells and plasma is concerned.

TABLE 9.—CASE 9. CHRONIC NEUTROPENIA WITH SPLENOMEGALY; WISEMAN-DOAN SYNDROME, 17.22 G. M., ♀, 52.

Source of blood	Hgb. in gm. per 100 cc.	Hem- atocrit %	RBC in mill. per c.mm.	WBC	MCH in m μ g.	MCC in %	MCV in cu. μ
Peripheral venous blood 4 hours preoperatively	10 5	34 5	3 75	1,200	28 0	30 40	108 7
Splenic artery	12 0	39 2	3 65	2,600	32 9	30 60	93 1
Splenic vein	12 8	40 0	4 15	2,900	30 8	32 00	103 7
Splenic vein after adrenalin	14 0	43 3	4 83	20,400	29 0	32 15	111 5

Spleen weight 1100 gm.

Microscopic: Touch preparations from the fresh spleen revealed occasional macrophages containing neutrophils. These were found in larger number in smears of the splenic vein blood, but not in those from the artery. Phagocytosis was not observed in the stained sections of the spleen fixed by injection of Helly's solution. The histologic structure was relatively normal. Moderate congestion of some of the sinuses was observed.

So far as can be determined, the present observations of the marked increase in hematocrit percentage in the splenic vein blood after adrenalin are the first to be recorded for man. Lauda and Haam¹³ noted an entirely similar hemoconcentration in the splenic vein blood of dogs after administration of adrenalin. Cruikshank's observations on the cat's spleen have already been referred to.⁶ It may be noted further that MacKenzie and his associates¹⁵ have recently described the rapid effect of adrenalin in emptying the pulp of the living cat's spleen of its erythrocytes.

The cause of the above noted reduction in hemoglobin concentration of the red cells cannot be stated with certainty. It is thought probable that an actual loss of hemoglobin from intact red blood cells has occurred during the period of their sequestration in the spleen. The question arose as to whether the reduced hemoglobin concentration of the cells might be only apparent, due perhaps to fragmentation of erythrocytes such as described by Rous and Robertson¹⁹ a number of years ago. Two points argue against this explanation. One is that the presence of fragments was not prominent nor did they appear to have increased after adrenalin as compared with before. In order to account for the marked lowering in hemoglobin concentration, it is believed that fragmentation should really have increased quite obviously. The second point is that the mean corpuscular volume did not vary significantly.

A marked increase might have been expected if fragmentation were important, since under these circumstances the erythrocyte count would be relatively lower than the hematocrit percentage (the fragments would still contribute to the latter, but often, at least, not to the former). An increase in MCV was not observed. Rather than fragmentation, it is thought that the intact or relatively intact erythrocytes suffered an actual loss of hemoglobin. v. Cziike⁶ was the first to observe that simple sterile incubation of red blood cells *in vitro* resulted in an appreciable degradation of hemoglobin to bile pigment. This observation was confirmed by Barkan^{1,2} who has shown that incubation of fresh sterile blood for as little as

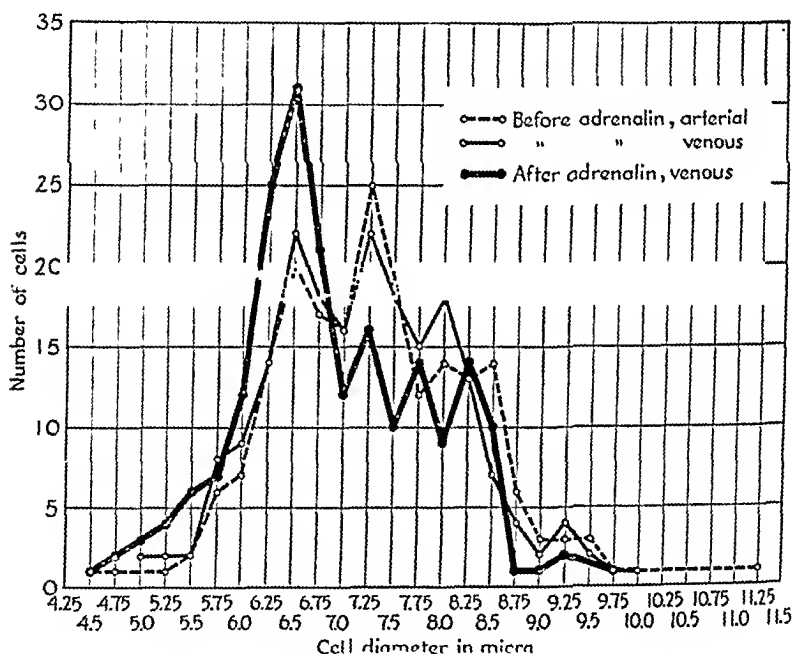


FIG. 1.—Price-Jones curves of splenic venous blood before and after adrenalin in Case 3.

6 hours results in significant increases of bilirubin and iron in the supernatant plasma. This phenomenon was correlated by Barkan with the presence of "pseudohemoglobin" and "easily split off" iron in the red blood cells. Barkan's "pseudohemoglobin" and Lemberg's "verdohemoglobin"¹⁴ are probably synonymous, indicating a bile pigment-iron-protein compound intermediary between hemoglobin and bilirubin. In this compound the porphyrin ring of the hemoglobin molecule has opened at the α -methene bridge with the result that a biliverdin-like substance is formed, still in close association with iron and protein. *In vitro*, at least, it has been possible to prepare bilirubin from hemoglobin by this type of transi-

tion.^{7,14} To what extent it is important in the *in vivo* formation of bilirubin has not yet been established.

In accordance with previous observations⁴ the present study has shown that the erythrocytes in the splenic vein are commonly somewhat more fragile than in the splenic artery, and that this is even more noticeable in the splenic vein blood after adrenalin. The increased spheroidicity correlated with this is typified in the data shown in Figure 1 (Case 3). Whether there is any direct relationship between this characteristic and the reduced hemoglobin concentration of the red blood cells is unknown. That there may be such a relationship is suggested by the fact that the erythrocytes become more spheroidal and less resistant to hypotonic saline on sterile incubation.^{3,9}

We have not yet given sufficient attention to the hematocrit percentage and hemoglobin concentration of the red cells in the peripheral blood before and at various intervals after adrenalin. Judging from the present data and from previous observations of hemoglobin and erythrocyte concentration (of the whole blood), it is likely that the reduction in hemoglobin concentration of the red cells as noted in the tables, could often be detected in the peripheral blood. Recently the following data were obtained in a case of aleukemic myelosis with massive splenomegaly:

TABLE 10.—PERIPHERAL BLOOD VALUES IN A CASE OF MYELOSIS BEFORE AND AFTER ADRENALIN

Time	Hgb. in gm. per 100 cc.	RBC in mill. per c. mm.	Hem- atocrit %	MCV in cu. μ	MCH in m μ g.	MCC in %
6-11-42						
Before adrenalin	10 30	3 41			30 2	
15 min. after adrenalin	10 60	4 13			25 7	
30 min. after adrenalin	11 20	4 81			23 3	
1 hour after adrenalin	10 70	4 62			23 1	
1½ hr. after adrenalin	10 00	3 72			26 9	
2½ hr. after adrenalin	9 25	3 04			30 7	
6-17-42						
Before adrenalin	10 15	3 75	33 6	89 8	27 0	30 0
30 min. after adrenalin	11 20	4 65	37 9	81 5	24 1	29 5
1 hour after adrenalin	11 20	4 98	39 1	78 5	22 5	28 6
4½ hr. after adrenalin	10 00	4 18	33 1	79 0	24 0	30 2

In this connection the results of Patek and Daland¹⁸ are of considerable interest. They were unable to establish "significant, sustained changes" of concentration on the basis of hemoglobin, erythrocyte, or hematocrit determinations. It should be noted, however, that they made observations at 5 and 15 minutes after adrenalin and then waited from 45 minutes to 3½ hours, usually 2 to 3 hours, before making additional observations. In our experience the significant increase in hematocrit, hemoglobin, and red blood cells is often not encountered until ½ hour after adrenalin. Little or no change may be observed if the intervals are much

shorter or longer than this, although in some instances the erythrocytosis may be distinct as early as 15 minutes after adrenalin. In Patek and Daland's study of 5 cases of familial hemolytic jaundice, only 1 had anemia, and it is noteworthy that this is the only one in which a significant post-adrenalin erythrocytosis was observed. The findings were as follows in this case:

TABLE 11.—PERIPHERAL BLOOD VALUES IN PATEK AND DALAND'S CASE

Time	Hgb. in gm. per 100 cc.	RBC in mill. per c.mm.	Hem- atocrit %	MCC in %*
Before adrenalin . . .	7.8	3.10	22.1	35.3
15 min. after adrenalin . . .	10.5	3.88	32.8	32.0
3½ hrs. after adrenalin . . .	7.9	3.00	21.6	36.5

* Calculated by us.

These data, together with the observations in the above case of aleukemic myelosis, suggest that the same red blood cells which enter the circulation at the height of the adrenalin effect, leave it again when the effect has passed. Since there is every reason to think that the spleen is the site of destruction of the more spheroidal erythrocytes, especially in hemolytic jaundice, in which the changes we are discussing are most striking, the likelihood is again supported that there is a direct relationship between increased spheroidocytosis and diminished hemoglobin concentration. Further studies correlating hematocrit percentage, hemoglobin, and red blood cell content and osmotic resistance, before and at suitable intervals after injection of adrenalin, are necessary to determine this point.

It may be noted that no correlation was observed between any particular histologic change in the spleen and the red cell concentration of the splenic vein blood or the hemoglobin concentration of its erythrocytes. In general, the most marked increases in hematocrit percentage and the most outspoken reductions of hemoglobin concentration in the red cells were observed when the spleen was large and congested. In Tables 4 and 6, however, it is seen that there was no evident congestion, yet the hematocrit percentage increased markedly while the hemoglobin concentration of the erythrocytes diminished. It is possible, of course, that splenic contraction might have been sufficient in these instances to expel most of the erythrocytes which had been present before the administration of adrenalin. The partial denudation of the sinus endothelium in many areas of the spleen of Case 4 (Table 4) might be indicative of a recent strong contraction with rapid emptying of the sinuses.

Summary and Conclusions. Studies of the splenic vein blood obtained at the time of splenectomy for various diseases have shown that in many instances a marked increase in erythrocyte concentration occurs after injection of adrenalin into the splenic artery. This increase is associated with a decrease in mean corpuscular hemoglobin concentration, and also with an increase in fragility

and spheroidicity. The exact cause of this decrease in hemoglobin concentration is unknown. It is believed that it may be due to an intracorpuseular degradation of a fraction of the hemoglobin in the intact erythrocytes during the period of their sequestration in the splenic pulp and sinuses, and quite analogous to that observed by Barkan when sterile blood is incubated.

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THE EFFECT OF THE ACCUMULATION OF BLOOD IN THE EXTREMITIES ON THE VENOUS PRESSURE OF NORMAL SUBJECTS.

BY JAMES V. WARREN, M.D.,

RESEARCH FELLOW IN MEDICINE, HARVARD UNIVERSITY.

AND

EUGENE A. STEAD, JR., M.D.,*

FORMERLY ASSOCIATE IN MEDICINE, HARVARD UNIVERSITY; ACTING PHYSICIAN IN
CHIEF, PETER BENT BRIGHAM HOSPITAL,
BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the
Department of Medicine, Harvard Medical School.)

PULMONARY edema from cardiac failure develops whenever the right ventricle pumps more blood into the pulmonary vessels than the left ventricle can pump out. Therefore, therapy is largely

* Dr. Stead is now Professor of Medicine at Emory University, Atlanta, Ga.

directed towards decreasing the output of the right ventricle. The venous return to the right ventricle may be decreased by quieting the patient with morphine, by phlebotomy and by the application of venous tourniquets to the extremities. The beneficial effect of the accumulation of blood in the extremities by venous tourniquets presumably results from a decreased venous return to the right ventricle as the result of a decrease in venous pressure. Many physicians have believed that in certain patients the accumulation of blood in the extremities by means of tourniquets is as effective as phlebotomy in the treatment of left ventricular failure. The purpose of this study was to determine whether in normal subjects venous accumulation in the extremities produced a significant decrease in venous pressure.

Method. Six normal young males served as subjects. All determinations were made with the subjects in the recumbent position. Twelve centimeter blood pressure cuffs were placed on the upper thighs as close to the trunk as possible. The cloth portion of the cuff was long enough to wrap around the thigh several times. Nineteen-gauge needles were inserted into the external jugular and antecubital veins and the resting venous pressure was recorded by the method of Moritz and Von Tabora⁶ using a point 5 cm. beneath the manubrium as the zero point. The needles were kept open by injecting a small quantity of saline at intervals. The blood pressure cuffs on the thighs were then inflated to a pressure of 85 mm. Hg. During this time the venous pressure was recorded every 30 seconds. At the end of 5 minutes the tourniquets were released. Venous pressure readings were recorded until they returned to the resting level.

TABLE 1.—EFFECT OF VENOUS TOURNIQUETS ON THIGHS AT PRESSURE OF 85 MM. HG ON THE VENOUS PRESSURE IN THE EXTERNAL JUGULAR AND ANTECUBITAL VEINS OF NORMAL SUBJECTS.

Subject:	VENOUS PRESSURE (mm. of H ₂ O).										
	1.		2.		3.		4.		5.		6.
	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.
Resting	100	110	100	135	105	110	105	115	80	110	
1 min. after tourniquets	65	55	80	115	90	100	80	100	70	85	
2 min. after tourniquets	50	75	60	110	75	100	70	100	45	60	
3 min. after tourniquets	45	75	45	110	70	105	70	95	46	40	
4 min. after tourniquets	40	70	40	110	65	105	70	95	25		
5 min. after tourniquets	40	70	35	110	65	100	70	100	25	50	
1 min. after release	95	110	..	115	100	105	100	115			
1 min. after release	105	120	..	125	105	..	95	110	75		
2 min. after release	100	120	..	130	105	..	95	..	80	110	

Results. In 6 normal subjects the average decrease in venous pressure in the external jugular vein produced by the application of venous tourniquets to thighs was 53 mm. of water, the extremes being 65 and 35 mm. of water. The venous pressure fell gradually, reaching a plateau after 2 to 4 minutes. After release of the tourniquets, the venous pressure rose rapidly, reaching the resting level in from 30 to 60 seconds (Table 1).

In 4 subjects the venous pressures in the antecubital and external jugular veins were measured simultaneously. In each instance the pressure in the antecubital vein was higher than that in the external

jugular vein. In these 4 subjects venous tourniquets produced an average fall in venous pressure of only 23 mm. of water in the antecubital vein, while the average decrease in the pressure in the external jugular vein determined at the same time was 50 mm. of water (Table 1).

The application of the venous tourniquets caused little discomfort. There was a slight increase in heart rate during the period of venous accumulation, but the arterial pressure showed little change.

Discussion. The pressure in the external jugular vein was always lower than that in the antecubital vein, and the application of venous tourniquets always produced a greater decrease in venous pressure in the external jugular than in the antecubital vein (Fig. 1). These observations are in accord with those of other investigators who have shown that the antecubital venous pressure does not always vary with the filling pressure of the heart, because the veins of the arm form a collapsible rather than rigid system of tubes.^{4,5} It has been demonstrated that no matter how much the intrathoracic pressure is decreased, the venous pressure in the antecubital vein remains positive.² The negative intrathoracic pressure collapses the walls of the veins as they enter the thorax and prevents the suction effect of the negative intrathoracic pressure from being transmitted to the blood in the antecubital vein. When the venous pressure is elevated, the column of blood in the antecubital vein becomes continuous with that in the great veins of the thorax. Under these conditions the vein does not collapse in any part of its course, and the pressure in the antecubital vein is the same as that in the right auricle.¹ When the venous pressure is lowered, the vein tends to collapse. It is reopened by the pressure of blood flowing into the antecubital vein from the hand and forearm. Under these conditions, the antecubital venous pressure may not reflect changes in venous pressure in the thorax or auricle. The above-mentioned factors have little influence on the pressure in the external jugular vein, because normally the jugular veins are somewhat distended in the recumbent position. Therefore, on theoretical grounds a decrease in the filling pressure of the right auricle because of a lowering of the venous pressure below the normal level would be expected to produce a greater fall in the pressure in the external jugular vein than in the pressure in the antecubital vein.

Accumulation of blood in the lower extremities by the application of venous tourniquets causes a significant lowering of the venous pressure in normal subjects. The fall in venous pressure is produced primarily by the increase in size of the venous bed in the extremities, although the slight decrease in plasma volume brought about by the high capillary pressure in the extremities may be a minor factor. Ebert and Stead³ measured the amount of blood present in one upper and two lower extremities before and after venous

congestion. They demonstrated that in the 5 subjects studied, an average of 700 cc. of blood was removed from the head, trunk and arm by placing venous tourniquets on one upper and two lower extremities. This is as much blood as is usually removed during a single venesection.

VENOUS TOURNIQUETS ON THIGHS

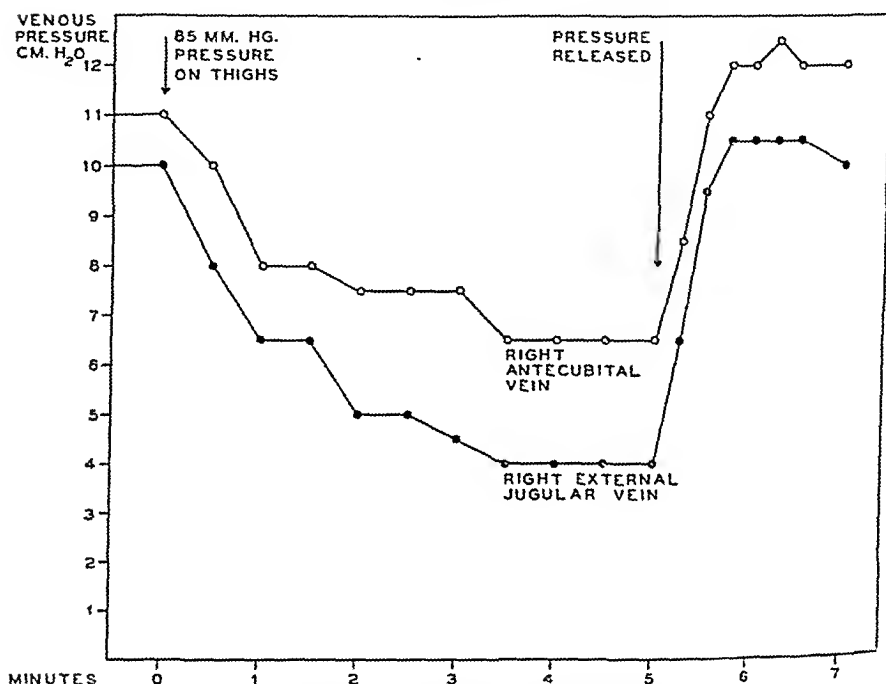


FIG. 1.—The effect of venous tourniquets on the pressure in the antecubital and external jugular veins of a normal subject.

It has been previously pointed out³ that venous tourniquets are more effective when the systemic venous pressure is normal, when edema of the extremities is absent, and when the patient has been in the recumbent position. If the venous bed in the extremities has already been distended by postural means or by a marked generalized increase in venous pressure, the application of tourniquets will produce little further increase in the size of the venous bed. If the legs are swollen tight with edema, the high tissue pressure will prevent the accumulation of large amounts of blood in the veins. Failure to recognize these limitations in the use of tourniquets accounts for the occasional report that venous tourniquets are ineffective in the treatment of acute left ventricular failure.

Summary. 1. Venous tourniquets at a pressure of 85 mm. Hg were applied to the upper thighs of 6 normal subjects.

2. The application of these tourniquets caused a decrease in

venous pressure in both the external jugular and antecubital veins. The average fall in venous pressure in the external jugular vein was 53 mm. of water. The average fall in venous pressure in the antecubital vein was 23 mm. of water.

3. The decrease in venous pressure from the application of tourniquets to the upper thighs is greater in the external jugular than in the antecubital vein, because the arm veins tend to collapse when the venous pressure is lowered. After the vein walls are in contact, further lowering of the venous pressure proximal to the point of collapse produces no further decrease in venous pressure in the distal portion of the vein.

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PYELOGRAMS IN PATIENTS WITH ESSENTIAL AND MALIGNANT HYPERTENSION

By J. C. SHRADER, M.D.

JOHN M. YOUNG, M.D.

AND

IRVINE H. PAGE, M.D.

INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital)

THIS study was undertaken in an attempt to answer certain questions in the interpretation of retrograde pyelograms of hypertensive patients who showed no evidence of "surgical" renal disease. These questions were: (1) Is there a pyelogram characteristic of hypertensives? (2) Is the incidence of abnormal urograms in an unselected group of hypertensives greater than in an unselected group of normotensive controls?

A. Characteristics of the Pyelograms of Hypertensives. Voelcker and von Lichtenberg made the first urograms in 1905 but a critical analysis did not appear until 20 years later when Eisendrath and Arens^{2,3} called attention to the existence of normal variations. They described three groups of normal pyelograms, *viz.*, ampullary, bifid and pseudospider. The ampullary proved to be the most common group (Fig. 1). When there were two rather distinct divisions of the pelvis from which branched one or more major calyces the pyelogram was classified as bifid (Fig. 5). Those whose calyces

were slender, elongated, and branching were classified as pseudospider (Fig. 4). They found the necks of the major and minor

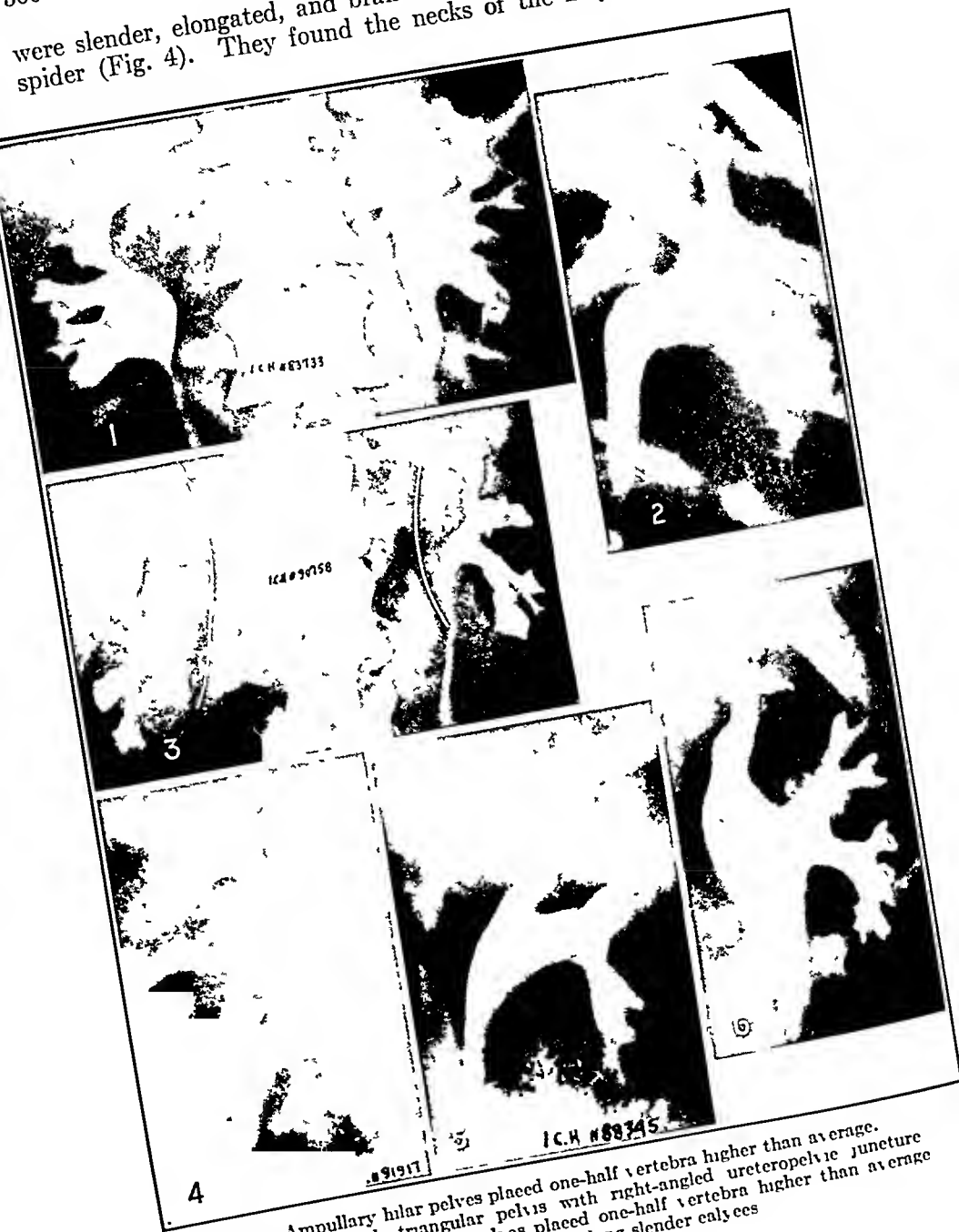


FIG. 1.—Ampullary hilar pelvis placed one-half vertebra higher than average.
 FIG. 2.—Horizontal, triangular pelvis with right-angled ureteropelvic juncture
 FIG. 3.—Bilateral intrarenal pelvis placed one-half vertebra higher than average
 FIG. 4.—Pseudospider type pelvis showing long slender calyces
 FIG. 5.—Bifid type pelvis.
 FIG. 6.—Extrarenal pelvis.

calyces were usually quite narrow but with much variation. The calyces could be so large that the pelvis proper was only visible as a small portion of the pyelogram, and conversely the pelvis often predominated over the calyces. Changes in shape of the ureter, pelvis and calyces due to peristalsis were emphasized.

In the same year Goldstein and Carson⁵ showed that normal ureters have diameters of 2 to 5 mm., and the normal pelvis measures 2 x 2 cm., with an average capacity of 8 ml. varying from 3 to 13 ml.

Moody and Van Nuys¹⁰ examined 450 healthy university students with antero-posterior roentgenograms of the abdomen and reported the most common position of the kidney to be opposite the first 4 lumbar vertebræ when erect. When supine, the cephalic pole lay opposite the 12th thoracic and the caudal pole opposite the 3d lumbar vertebræ.

In 1933 Rose, Hamm, Moore and Wilson,¹⁸ from a critical analysis of 385 pyelograms defined a normal renal pelvis as one symmetrically placed in the kidney, with free flow of urine through its parts.

The so-called "intrarenal" pelvis may be defined as one in which the renal tissue wholly surrounds it and the ureteropelvic juncture is seen in the Roentgen photograph as part of the medial border of the shadow of the kidney (Fig. 3). By contrast, the ureteropelvic juncture in a kidney with a "hilar" pelvis is separated from the medial border with the pelvis partly within it. Occasionally the pelvis appears to be outside the kidney, making the intrarenal portion seem to consist entirely of calyx ("extrarenal" pelvis) (Fig. 6).

Method. In an attempt to answer the first question we have limited our study to patients with *normal* retrograde pyelograms as judged by the criteria suggested by the authors cited above, and by Wesson and Ruggles.²⁵ The borderline between normal and pathologic, in brief, depends upon a separation of all pyelograms exhibiting signs of stasis, infection, displacement, lithiasis, filling defect, or congenital anomaly. These criteria will be discussed more fully in the section on results. In order to facilitate analysis, each pyelogram was inspected for certain characteristics:

1. Location of renal pelvis as to whether it was intrarenal, extrarenal, or hilar.
2. Level of renal pelvis in relation to vertebral landmarks.
3. Renal torsion; complete or incomplete rotation.
4. Presence or absence of a right-angled ureteropelvic juncture.
5. Capacity of the pelvis as judged from the comparative size of the shadow.*
6. Size of calyces in relation to pelvic size.
7. Number of minor calyces.
8. Configuration of calyces and infundibuli.
9. General shape of pelvis; triangular, square or rounded.
10. Axis of renal pelvis; normal oblique, horizontal or vertical.
11. Tendency toward intrarenal duplication of pelvis (bifid pelvis).

* Retrograde pyelograms were made by the gravity method.

The retrograde pyelograms of 100 hypertensive patients were compared with the pyelograms of 100 normotensive individuals. Most of these were made by one of us (J. M. Y.) and were considered to be within normal limits by the roentgenologist, the urologist and the authors of this paper.

We arbitrarily selected 149 mm. systolic and 89 mm. Hg diastolic as the upper limits of normal arterial pressure.

Results. The results are summarized in Table 1.

1. The renal pelvis of adults is usually hilar and in this, hypertensive subjects do not differ from normotensives. Further, the difference in the incidence of bilateral intrarenal pelvises is only 4%. When those with unilateral intrarenal pelvises are included, the difference is 3%.

2. The ureteropelvic juncture usually is at the level of the 2d lumbar transverse process with the right pelvis placed 2 or 3 cm. below the left. The limits of normal motility were set at one vertebra above and below this point. Very few pyelograms were seen where the juncture was higher than the 1st lumbar transverse process when supine. Those in which the juncture fell below a line through the 3d transverse processes when supine or erect were classified as abnormal. Occasionally, even though the kidney did not descend this low when erect, angulation of the ureter indicated an abnormal degree of ptosis.

The series is too small for statistical analysis but it is noteworthy that kidneys placed lower than average occurred twice as frequently in hypertensives and higher than average on one or both sides in 42% of normotensives, as compared to 30% in the hypertensives.

3. Renal torsion apparently is the result of incomplete rotation of the kidney. It was present in 11% of hypertensives and 8% of normotensives. We believe that partial rotation is a normal variation if unassociated with signs of stasis or infection. Dilatation of the calyces (calyectasis), dilatation of the pelvis (pyelectasis), or blunting of the calyces were regarded as signs of stasis, and shagginess or blurring of the calyceal outline as signs of infection.

4. When the axis of the pelvis meets the ureter at approximately a 90 degree angle it is designated a right-angled ureteropelvic juncture (Fig. 2). Such pelvises usually have a horizontal axis and are roughly rectangular in shape. If, with this finding stasis was suggested by high insertion of the ureter, aberrant renal blood-vessel, calyectasis, ptosis, ureteropelvic stricture or an angle of less than 90°, the pyelogram was considered abnormal. The incidence of right-angled ureteropelvic junctures was the same in each class of patients.

5. The average capacity of the renal pelvis is generally believed to be 6 to 9 ml. Otherwise normal pelvises may hold as much as 20 ml. In reading pyelograms it is customary for urologists and roentgenologists to make a notation if the pelvis appears small or

large. Wesson and Ruggles²⁵ advise against interpreting the outline of a pelvis as abnormal unless the evidence of pyelctasis is beyond question. We distinguish early hydronephrosis from a pelvis which is merely large by the presence of blunting of the calyces and/or bulging as indicated by convex superior and inferior borders. Such pyelograms were considered abnormal. Normal pyelograms were grouped according to the relative size of their pelvises.

Non-hydronephrotic pelvises larger than average were found almost twice as frequently in hypertensives.

6. We noted the size of the pelvis in relation to the size of the calyces because it has been suggested,^{18,25} that a pelvis small in proportion to the calyces tends to cause back pressure. Pyelograms which showed large branching major calyces with comparatively small pelvic reservoirs were classed as smaller than average. Those films that showed short, stubby minor calyces with indefinite major calyces, so that the pyelogram seemed to be almost all pelvis were recorded as larger than average. A pelvis of average size in relation to the size of the calyces occurred with equal frequency in hypertensives and normotensives.

7. The minor calyces may vary in number from 6 to 15.⁷ In a retrograde pyelogram it is difficult to count them all as a few may be obscured. We arbitrarily considered those showing between 8 and 13 minor calyces per kidney as exhibiting an average number. There was no significant relationship between the number of minor calyces and the existence of hypertension.

8. The superior calyx is usually long and thin while the inferior calyx is often short and stumpy.²⁵ The position of the pelvis within the kidney affects the length of the major and minor calyces. There are definite changes in the size and contour of the calyces, due to their peristaltic activity—short and broad calyces becoming long and narrow. Therefore, variations in the configuration of the calyces may not be regarded as permanent. A narrow, elongated infundibulum may merely be a transient peristaltic wave and not an impediment to drainage. Irrespective of these difficulties in interpretation we thought it interesting to record the character of the calyces. There was no relationship between the pelvic configuration and hypertension.

9. As seen in Figure 1 the renal pelvis has a triangular outline. The base of the triangle parallels the long axis of the kidney. In certain pyelograms the pelvis assumes a rectangular appearance while more rarely the outline is rounded and roughly spherical. In both hypertensives and normotensives the general shape of the pelvis was triangular in 9 out of 10 pyelograms.

10. The axis of the pelvis corresponds to the height of the pelvic triangle. This usually meets the axis of the ureter at an angle of 130 to 150 degrees. If the angle is more acute than this we have classed it as a horizontal pelvis. If the angle approaches 180 de-

grees, the pelvis is classed as vertical. The pelvic axis of hypertensives does not differ from normotensives.

11. A bifid pelvis is one showing a tendency to intrarenal duplication in that there are two divisions of the pelvis from each of which may branch 1 to 3 major calyces. There is no significant difference in the incidence of bifid pelvis in the two classes of patients.

TABLE 1.—SUMMARY OF ANALYSIS OF NORMAL PYELOGRAMS OF 100 HYPERTENSIVES AND 100 NORMOTENSIVES

Pyeelographic characteristics	Classification of normal variations	Number	
		Hypertensives	Normotensives
1. Location of renal pelvis	Hilar pelvis bilaterally	59	62
	Intrarenal pelvis bilaterally	20	16
	One hilar, the other intrarenal	16	17
	Extrarenal	3	4
	Uncertain	2	1
2. Level of renal pelvis	Average level	53	48
	Higher than average { Unilat.	10	14
	Bilat.	20	28
	Lower than average { Unilat.	10	3
	Bilat.	5	4
	One pelvis high, other low	2	3
3. Renal torsion (kidney rotation)	Complete rotation	89	92
	Incomplete rotation { Unilat.	11	8
	Bilat.	0	0
4. Presence of right-angled ureteropelvic junct	Normal ureteropelvic juncture bilaterally	76	78
	Right-angled ureteropel. junct. bilaterally	7	3
	Unilat. rt-angled ureteropel. junct. { R	15	18
	L	2	1
5. Capacity of renal pelvis	Average	61	66
	Smaller than average	21	24
	Larger than average	18	10
6. Size of pelvis in relation to size of calyces	Average	64	65
	Smaller than average	22	19
	Larger than average	14	16
7. Number of minor calyces	Average	92	89
	More than average	3	6
	Fewer than average	5	5
8. Character of calyces	Not unusual	63	63
	Predominance of long, narrow infundibuli	22	24
	Predominance of short, stubby calyces	15	13
9. General shape of renal pelvis	Triangular pelvis bilaterally	90	92
	Rectangular pelvis { Unilat.	8	2
	Bilat.	0	2
	Rounded pelvis { Unilat.	1	4
	Bilat.	1	0
10. Axis of renal pelvis	Normal axis bilaterally	67	69
	Horizontal { Unilat.	13	15
	Bilat.	10	10
	Vertical { Unilat.	7	5
	Bilat.	2	0
	One horizontal, other vertical	1	1
11. Type of renal pelvis	Neither pelvis bifid	72	67
	Bifid pelvis { Unilat.	11	12
	Bilat.	17	21

B. Incidence of Renal Abnormalities in Essential and Malignant Hypertension. In order to determine whether abnormalities of the urogram are more common in hypertensive than in normotensive patients, we considered the following data:

1. The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as judged by retrograde pyelograms.

2. The incidence of the same degree of renal abnormalities in an unselected group of hypertensive patients.

3. The average mean arterial pressure of patients with abnormal pyelograms as compared with the average mean pressure of those with normal pyelograms.

To determine the correlation between abnormal pyelograms and associated elevated arterial pressure, we reviewed 218 consecutive retrograde pyelograms made at the Indianapolis City Hospital during the past year. Each pyelogram was classified as normal or abnormal and the blood pressure of the patient noted. Retrograde urography is performed routinely on all hypertensive patients studied at the Lilly Clinic. This group was considered separately from the above.

Results. One hundred pyelograms exhibiting obvious abnormalities such as hydronephrosis, ptosis, filling defects, polycystic disease, ureteropelvic constriction, calculus or congenital anomalies were studied. Of this group, 78 were normotensive and 22 were hypertensive. Criteria for the occurrence of hypertension in the general population seldom are the same, thus making it difficult or impossible to compare one investigation with another. Our problem was to determine the incidence of hypertension in the population of a general hospital. Whether this differs from that in the supposedly healthy civilian population we do not know. Braasch, Walters and Hammer¹ found that 19.4% of 869 admissions to the Mayo Clinic (ages 20 to 70) had systolic pressures of 145 mm. of mercury or above. Oppenheimer, Klemperer and Moschkowitz¹¹ selected every 15th patient in a series of 5000 who came to autopsy and observed high blood pressure in 24%. In general, a blood pressure of 155/95 mm. Hg or more was considered the criterion of hypertension. Shure²³ selected at random 947 of 11,898 autopsy reports and found 34.9% had a persistent arterial pressure of 150/95 or above.

Recognizing that there is no general agreement as to the incidence of hypertension we believe that an incidence of 22% in our 100 patients with abnormal urograms (age group 20 to 60) is not significantly greater than that in the general hospital population.

The average arterial pressure of 122 patients with gross renal abnormalities as judged by retrograde urography was compared with the average arterial pressure of 96 persons with normal pyelograms. The results were summarized in Table 2.

The urograms of 114 unselected patients who came to the Lilly Clinic complaining of hypertension were reviewed and classified. The results are summarized in Table 3. The borderline cases were those with questionable blunting of the calyces, or questionable dilation of the pelvis and calyces.

Unfortunately it is practically impossible to find a comparable control series because the number of normotensives showing significant renal abnormalities is high in those who must be cystoscoped.

Comment. A normal pyelogram does not conclusively rule out the presence of renal disease, but when abnormal it usually indicates a moderately extensive lesion. The interpretation of pyelograms is often uncertain due to lack of generally accepted limits of normalcy. This paucity of normal criteria is partly due to limitations of description. The aphorism, "One picture bespeaks a thousand words," is nowhere more apt.

TABLE 2.—COMPARISON OF AVERAGE ARTERIAL PRESSURES OF PATIENTS WITH ABNORMAL AND WITH NORMAL PYELOGRAMS

	Average systolic arterial pressure, mm. Hg	Average diastolic arterial pressure, mm. Hg	Average mean arterial pressure, mm. Hg
122 patients with grossly abnormal pyelograms	129	81	105
96 patients with normal pyelograms . . .	131	81	106

TABLE 3.—PYELOGRAMS OF 114 HYPERTENSIVE PATIENTS

	No.	%
Normal	84	73 68
Borderline	8	7 03
Abnormal	22	19 29
Total	114	100 00

Retrograde urography has certain well-known advantages over the excretory method. Minor degrees of deformities are delineated more clearly. According to Wesson and Ruggles,²³ "One who depends upon intravenous pyelograms alone and does not check the diagnosis by a complete kidney investigation is going to make costly blunders."

Ravich¹⁵ using this method concluded that hypertension is almost invariably associated with kidneys having an intrarenal pelvis. In our series 61% of hypertensives failed to show an intrarenal pelvis. Sarnoff²⁴ reported an incidence of 40% intrarenal pelvis in 50 hypertensives. Hyman and Schlossman⁶ found no higher incidence among hypertensive than normotensive patients.

Riskind and Greene¹⁶ recently reported a case of hypertension associated with postural unilateral renal torsion. We have found 4 normotensives who exhibited unilateral failure of rotation plus signs of stasis of a degree to be considered abnormal. Our series suggests that incomplete rotation occurs with equal frequency in normotensives.

Attempts have been made to classify all cases of essential hypertension according to the predominant associated syndrome. Williams and Harrison²⁵ and Schroeder and Steele²⁰ distinguish five groups: (1) renal; (2) nervous; (3) vascular; (4) endocrine; and (5) unclassified. This follows the classification of Page¹² except for the fifth group which is limited to essential and malignant hypertension. McCann⁹ goes so far as to hypothesize that in 80% to 85% essential hypertension depends on atheromatous narrowing of the

larger renal arteries and in the remainder the trouble is due to unsuspected disorders of the kidneys or urinary passages.

Schroeder and Steele²¹ found excretory urographic abnormalities in 50 of 71 essential hypertensives. In another series of 178 cases²² which includes these 71 patients, 71 (45%) showed abnormal excretory urograms. Schroeder¹⁹ considered as abnormal 37 intravenous urograms of 50 patients exhibiting slight elevation of blood pressure. Slight hydronephrosis was the most frequent lesion noted. Our results differ from theirs in two regards: (1) the incidence of hypertension in a hospital population is believed by us to be greater than suggested by them, and (2) our results were obtained by comparing a normal with a hypertensive group of patients.

Braasch, Walters and Hammer¹ found the incidence of hypertension among 1684 patients with surgical condition of the kidney to be no higher than in a similar group of people taken at random. Friedman, Moschkowitz and Marrus⁴ showed that the mean blood pressure and incidence of hypertension was no greater in a group of 193 patients nephrectomized for unilateral renal disease than in a comparable control series.

Maher and Wosika⁸ found only 17% of 600 patients with hypertension to have abnormalities of the urinary tract and kidneys of sufficient degree to remove them from the category of essential hypertension. The specific lesions included prostatic hypertrophy as the most frequent, pyelonephritis, urolithiases and combinations of obstruction and infection. It is noteworthy that such conditions usually are expressed by urographic anomalies especially if they have progressed to such a degree as to contribute to, or cause, hypertension. Therefore, the urogram should be a fairly reliable method for detecting such cases.

Pearman, Thompson and Allen¹⁴ present evidence indicating an incidence of renal lesions of 3.2% in 12,000 instances of hypertension.

Palmer, Chute, Crone and Castleman¹³ reported significant urographic abnormalities in 22% of 212 hypertensives.

Ritter¹⁷ observed hypertension in 14.2% of 28 patients with urinary developmental anomalies. He reviewed the histories of 24 patients suffering from hydronephrosis or renal anomalies with or without stone or secondary infection and found none to be hypertensive after an interval of 5 to 10 years.

It is our impression that the range of normal variation in urograms is wider than usually recognized. Questionable pyelographic variations in normotensives are often disregarded while the same variations in hypertensives are emphasized—the patient then becoming a "renal" hypertensive.

Summary and Conclusions. The retrograde pyelograms of 100 hypertensives and 100 normotensives were studied to ascertain whether hypertension was associated with any constant pyelographic variation. Those which seemed more common in hypertensives

were: (1) renal pelves which were larger than average, and (2) pelves whose position was lower than average. Intrarenal pelvis, incomplete rotation (renal torsion), right-angled ureteropelvic junction, and bifid pelvis were no more common than in normotensive patients. Hypertension was not associated with any significant variation in the size of the pelvis to the size of the calyces, the general configuration of the pelvis, the pelvic axis, nor the number or morphology of minor calyces.

The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as demonstrated by retrograde pyelograms was 22%. The average mean arterial pressure of patients with abnormal pyelograms was the same as the average mean pressure of those with normal pyelograms. The incidence of significant renal abnormalities in an unselected group of hypertensives was 19%.

The retrograde pyelograms of patients with essential hypertension do not differ significantly from those of normotensives. The incidence of urographic abnormalities in an unselected group of hypertensives appears to be no greater than in normotensives.

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CARDIAC CIRRHOSIS

BY CURTIS F. GARVIN, M.D.

ASSISTANT PROFESSOR OF MEDICINE, WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE; VISITING PHYSICIAN, MEDICAL SERVICE, CLEVELAND CITY HOSPITAL, CLEVELAND, OHIO

(From the Department of Medicine of Cleveland City Hospital and Western Reserve University School of Medicine)

CARDIAC cirrhosis usually is defined as hepatic fibrosis due to congestive heart failure.^{1,2} In order to preclude the possibility that borderline cases might be included, this study of cardiac cirrhosis was limited to instances of hepatic fibrosis of such a degree as to cause actual architectural distortion of the liver. All cases of Laennec's cirrhosis and fibrosis due to infection were excluded. Only patients who died of congestive heart failure were studied, in order that there could be no question of the likelihood that significant passive hyperemia of the liver had been present.

The material for the study consisted of the clinical and pathologic observations on 790 consecutive, adult, autopsied patients in whom heart disease was the chief cause of death. These cases occurred in 6548 consecutive postmortem examinations done at the Cleveland City Hospital in the decade from January 1930 to December 1939 inclusive. Thirty-five instances of cardiac cirrhosis were encountered.

The Incidence of Cardiac Cirrhosis in Various Types of Heart Disease. The incidence of cardiac cirrhosis varied with the type of heart disease (Table 1). It is evident that cardiac cirrhosis occurred most often in rheumatic heart disease and hypertensive heart disease. Thus 119 patients who died primarily of rheumatic heart disease included 14 (11.8%) with cardiac cirrhosis. Of 264 patients who died primarily of hypertensive heart disease, 14 (5.3%) had cardiac cirrhosis. The remaining 407 patients (who died of a variety of other types of heart disease) included 7 instances of cardiac cirrhosis (1.7%).

Clinical Features. *Number of Episodes of Heart Failure, Splenomegaly, Ascites, Valvular Lesions and Jaundice.* The number of cases is not large enough to permit statistical analysis, but certain tendencies are demonstrable.

There was a tendency for cardiac cirrhosis to occur in patients who had had more than one episode of heart failure. The 14 patients with cardiac cirrhosis who died of rheumatic heart disease included 9 (64%) who had had more than one episode of heart failure. The remaining 105 patients who died of rheumatic heart disease but who did not have cardiac cirrhosis, included 38 (36%) who had had multiple failures. Of the 14 patients dying of hypertensive heart disease and showing cardiac cirrhosis, 6 (43%) had had more than one episode of heart failure. Of the 250 patients who died of

hypertensive heart disease and who did not have cardiac cirrhosis, 69 (28%) had more than one episode of heart failure.

There likewise was a tendency for splenomegaly to be associated with the cases of cardiac cirrhosis. This was best shown in the group of patients dying of rheumatic heart disease. Of the 14 patients with cardiac cirrhosis, 11 (79%) had a spleen weighing over 200 gm. whereas of the 105 patients without cardiac cirrhosis 26 (25%) had a spleen weighing over 200 gm.

In regard to ascites, in the rheumatic heart group, of the 14 patients with cardiac cirrhosis, 11 (79%) had ascites either clinically or at autopsy. Of the 105 patients without cardiac cirrhosis, 45 (43%) had ascites either clinically or at autopsy. In the case of the patients dying of hypertensive heart disease, of the 14 suffering from cardiac cirrhosis, 9 (64%) had ascites; of the 250 who did not have cardiac cirrhosis, 100 (40%) had ascites.

Study of the nature of the valvular lesions in the 119 patients who died of rheumatic heart disease showed that of the 14 who had cardiac cirrhosis, 4 (29%) also showed tricuspid stenosis. Of the 105 patients without cardiac cirrhosis, only 9 (9%) had tricuspid stenosis. Stated differently, of the 13 patients who had tricuspid stenosis, 4 (31%) had cardiac cirrhosis.

Jaundice did not occur frequently enough to permit study.

Diagnosis. It is difficult to diagnose cardiac cirrhosis clinically. The material at hand seems to indicate that the condition occurs more often in patients with heart disease of some standing. It occurs especially in patients with rheumatic heart disease or hypertensive heart disease, and relatively often in individuals with tricuspid stenosis.

The presence of a liver smaller than one would expect in the face of congestive failure, the existence of ascites and splenomegaly not attributable to other causes are suggestive evidence. However, in the clinical appraisal of a given case, this evidence could be misleading since all of these signs can occur in a patient without cardiac cirrhosis.

In the 35 cases studied, the diagnosis was made in only 5 cases. The report of the case in which the clinical diagnosis seemed most justified is as follows:

Case Study. J. G., a colored man aged 42, entered Cleveland City Hospital January 5, 1934. He had had shortness of breath on exertion and occasional swelling of the ankles for 8 months.

Examination showed a well-developed, well-nourished negro. He was short of breath. The cervical veins were distended. There were râles at the bases. The heart was enlarged in all directions and showed a systolic murmur at the apex. The cardiac mechanism was normal. The blood pressure was 220 systolic and 140 diastolic. The liver was tender and the edge was 6 cm. below the costal margin. There was no ascites. The extremities, scrotum, sacral and lower abdominal regions showed pitting edema. The retinal arteries were thin and tortuous, and venous nicking was present.

The patient received digitalis and diuretics, and improved. He was discharged February 10, 1934. The diagnosis was hypertensive heart disease and myocardial insufficiency.

He was again admitted to the hospital July 17, 1934, because of marked myocardial insufficiency. The findings were as before except that ascites was present. He improved and was discharged November 22, 1934.

The patient was admitted to the hospital the third time April 23, 1935. There was evidence of marked myocardial insufficiency. Abdominal paracentesis was done on 2 occasions. The edge of the liver was 5 cm. below the costal margin. He was discharged May 27, 1935.

He was admitted to the hospital a fourth time July 30, 1935. Shortness of breath and anasarca had returned. During this admission, because of ascites which recurred despite the frequent use of mercurial diuretics, abdominal paracentesis was done 9 times. The patient finally became free of edema, and was discharged February 22, 1936. The diagnosis of cardiac cirrhosis was made on this admission.

The patient was admitted to the hospital the fifth time April 17, 1936. He was moribund and died in 12 hours.

In a period of about 28 months, the patient had spent 407 days in the hospital. He had suffered varying degrees of myocardial insufficiency for over 3 years. The clinical diagnosis was hypertensive heart disease, myocardial insufficiency and cardiac cirrhosis.

Autopsy. Autopsy was performed by Dr. Gallavan 83 hours after death. The body was normally developed and showed marked anasarca.

The abdominal cavity contained 6300 cc. of serous fluid, the right pleural space 125 cc., the left pleural space 130 cc., the pericardial sac 300 cc.

The heart weighed 850 gm. and was dilated. The coronary arteries showed rather marked arteriosclerosis.

The liver was of normal shape and weighed 1875 gm. The edges were moderately rounded. The capsule was opaque and thickened. The organ cut with increased resistance. The surface was a mottled brownish-red color. It was difficult to distinguish hepatic lobules.

The other viscera showed chronic passive hyperemia. There was generalized arteriosclerosis.

TABLE 1.—THE FREQUENCY DISTRIBUTION OF CARDIAC CIRRHOSIS IN THE VARIOUS TYPES OF HEART DISEASE

Type of heart disease	No. of cases	No with cardiac cirrhosis	%
Hypertensive heart disease .	264	14	5.3
Coronary heart disease . .	177	3	1.7
Rheumatic heart disease .	119	14	11.8
Syphilitic heart disease .	67	1	1.5
Cor pulmonale .	54	1	1.9
Subacute bacterial endocarditis	31	0	0.0
Acute bacterial endocarditis .	13	0	0.0
Thyroid heart disease . .	9	0	0.0
Calcific aortic stenosis .	9	0	0.0
Obliterative pericarditis . .	7	1	14.3
Tuberculous pericarditis	7	0	0.0
Pericardial adhesions	5	1	20.0
Miscellaneous .	9	0	0.0
Undiagnosed .	19	0	0.0
	790	35	4.4

Microscopically, the architecture of the individual lobules of the liver could be made out but there was considerable distortion due to extensive fibrosis. This fibrous tissue was in most situations quite young as it stained poorly with Van Gieson's stain but vividly with Heidenhain's stain. The

fibrosis was most marked in the subcapsular areas where it was diffuse. Otherwise there was no constant distribution. There was considerable chronic passive hyperemia and the central veins were markedly distended.

The diagnosis was generalized arteriosclerosis, dilatation, cardiac cirrhosis* and chronic passive

Summary. Of 790 consecutive, adult, autopsied patients who died of heart disease, 35 (4.4%) had cardiac cirrhosis. Only those cases were included in which there was actual architectural distortion of the liver.

Cardiac cirrhosis occurred essentially in two types of heart disease, *viz.*, rheumatic heart disease (14 of 119 cases) and hypertensive heart disease (14 of 264 cases).

From a clinical standpoint there was a tendency for the cases of cardiac cirrhosis to be associated with multiple episodes of failure, ascites, splenomegaly and in the rheumatic group with tricuspid stenosis. In 5 of the 35 cases studied, the diagnosis was suspected clinically. It appears that there are no definite criteria, however, which permit the consistent clinical diagnosis of cardiac cirrhosis.

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STUDIES ON THE PENETRATION OF SULFONAMIDES INTO THE SKIN

I. PENETRATION OF SULFONAMIDES FROM VARIOUS OINTMENT BASES INTO THE INTACT SKIN OF GUINEA PIGS; AND A NEW METHOD OF ANALYSIS OF TISSUE SULFONAMIDES†

BY ERNEST A. STRAKOSCH, M.D.

FELLOW IN DERMATOLOGY

AND

WILLIAM G. CLARK, PH.D.

ASSISTANT PROFESSOR, DEPARTMENT OF ZOOLOGY, UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINN.

(From the Division of Dermatology and Syphilology; and the Department of Zoology, University of Minnesota)

In a previous paper,² we presented the first analytical data, to our knowledge, on rates of penetration of sulfonamides into the intact skin from various vehicles. These data were derived from

* Diagnosis of Dr. H. T. Karsner, Chief of the Department of Pathology of Cleveland City Hospital.

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direct tissue analyses of the skin of rabbits, rats and humans, after various periods of applications of sulfonamides in wet packs, ointments, and by iontophoresis.

One of us⁴ had previously attempted to determine the degree of liberation of the incorporated sulfonamide from various ointment and jelly bases into agar plates streaked with staphylococci, as judged by measured clear areas free of bacterial growth. It is now realized that this approach cannot be justifiably extended to clinical practice, since it shows only the partition coefficient between the vehicle and the agar. Although it does give some information regarding the degree of liberation of the incorporated sulfonamide, this information does not necessarily apply to the skin. Since it is of practical importance to have a better comparison of what can be obtained regarding the tissue concentration of sulfonamides diffusing from various vehicles, it was decided to examine the tissue concentrations produced by various ointment bases containing different concentrations of sulfonamides.

From the previous report² it was indicated that in regard to penetration of sulfonamides, rat skin was more similar to human skin than the more delicate rabbit skin. As it was impossible for the purposes of this study to use human subjects, because of the large number of cases needed, and the multiple biopsies required for each subject, we selected guinea pigs rather than the rat, as it was impossible to keep dressings or bandages on rats. Several experiments with rats immobilized in confining cages showed skin penetration rates of sulfanilamide quite comparable with those of guinea pigs and humans.

Methods. The experimental animals were guinea pigs ranging in body weight from 400 to 600 gm. The hair along the back and sides was clipped with a fine electric hair clipper, taking care not to injure the skin. The ointments were applied to the skin and held in place with gauze bandages and adhesive tape. The animals were placed in narrow confining cages which made it impossible for them to disturb the bandages, yet permitted them to take food (cabbage) placed before them. In order to study the effect of time and concentration on penetration, ointment was applied to two areas, separated by the vertebral column. These areas extended along the sides of the animal, precautions being taken to prevent the ointments applied to each area, from intermixing. The ointments were reapplied once daily.

Biopsies were performed after 1, 2 and 3 days, to obtain the time effect. When concentration effects were being studied, ointments of two different concentrations of sulfanilamide (SNA)* were applied to the same animal, one on the left area, and the other on the right.

Prior to performing biopsies, the animals were thoroughly washed with soap and warm running water, after which the areas to be biopsied were shaved and rinsed. A piece of skin approximately 4 to 8 sq. cm. was removed with scissors under light ether anesthesia, cutting down to the panniculus carnosus muscle layer. The excised skin pieces were washed

* Supplied through the courtesy of Dr. D. F. Robertson, of Merck & Co., Inc., Rahway, N. J.

with soap and running warm water, blotted, and pinned to sheet cork. Uniform skin aliquots weighing approximately 60 to 100 mg. were punched out by means of a sharp blow delivered to a cylindrical brass punch, approximately 1 cm. in diameter. They were weighed immediately on a torsion balance and analyzed for total sulfanilamide.

Method of Chemical Analysis of Tissue Sulfanilamide. Tissue SNA was first determined by a method previously described,² in which free SNA was analyzed in tissue filtrates from ground tissue, by the method of Bratton *et al.*,¹ using a photoelectric colorimeter.

The photoelectric colorimeter was designed and built after the Evelyn type instrument.³ It contained a Mazda flashlight bulb and metal reflector as the light source, controlled in intensity by a vernier rheostat combination; a General Electric barrier type photoelectric cell,* linear within 1% up to 50 microamperes (the maximum photoelectric current generated was less than 3 microamperes); and a Leeds-Northrup galvanometer (type KS5410), with a period of 3 seconds or less, a resistance of ca. 1000 ohms, a critical damping resistance of 5000 to 10,000 ohms, and giving a full-scale deflection at 2.5 microamperes. The entire instrument, including the galvanometer and lamp and scale, is housed in a small box, 9 x 7 x 13 inches, and cost approximately \$100 to construct. The aluminum house holding the light source, filter holders, absorption cuvette, and photoelectric cell, is similar to that described by Evelyn³ except that the filter holder was adapted to hold the less expensive Standard Corning and Wratten 2 inch filters, and the cuvette holder contained a microadaptation for smaller test tube cuvettes, of dimensions 11 mm. inside diameter, 1 mm. wall thickness, 10 cm. long, and optically selected. Readings could be made with 3 cc. volumes.

Bratton *et al.*¹ describe the absorption maximum of SNA solutions after color development by their method, which is essentially the method we used, as 5450 Å units, whereas we found it to be 5421 Å, as determined both in a special Zeiss single monochromator photoelectric spectrophotometer, and in the Coleman single monochromator spectrophotometer. The curve was quite broad, however, varying not more than 2% transmission from the maximum when extended 50 Å units in either direction from the maximum. When we chose a Corning filter combination which gave a maximum transmission close to the absorption maximum of the SNA solution, namely 5425, difficulty was had because the filter absorbed too much light, and a good curve could not be obtained. Finally a filter combination of Corning filters No. 3486, 5120, and 4303, was selected, which followed Beer's law with standard SNA solutions, up to 0.3 mg. % concentration. This filter combination gave a maximum transmission at 5521 Å units, varying only about 2%

* General Electric Catalogue No. 4120833-9-1.

transmission when shifted 50 Å units in either direction from the maximum.*

In determining large numbers of tissue SNA concentrations, it was found time-consuming and cumbersome to grind the tissues, especially skin, in a mortar with sand, prior to filtration and analysis, as described previously.² Hence another method of analysis was developed, which permitted large numbers of determinations to be made each day. Tissue aliquots are macerated and taken into solution by HCl hydrolysis in a hot water bath, cooled, precipitated with trichloroacetic acid, filtered, and the filtrate analyzed for SNA.

Procedure. The weighed biopsy was placed into a 10 cc. volumetric flask, 3.5 cc. 0.6 N HCl were added from a burette, and the flask partially immersed in a boiling water bath, by means of a wire basket holder, for 30 minutes, after which the tissue was completely macerated and taken into solution upon vigorous (!) shaking. Longer boiling tends to produce discoloration, and subsequent errors. Two cc. 15% trichloroacetic acid was added, making the solution 3% in trichloroacetic acid, and the flask filled to volume with distilled water. After thoroughly shaking, the solution was filtered through a fine grained analytical filter paper (7 cm. No. 589 ashless Schleicher and Schüll) in a 1.5 inch short-stemmed funnel. Five cc. of the clear filtrate was analyzed for SNA by the method of Bratton *et al.*,¹ modified to meet the conditions of our experiments. To 5 cc. of the filtrate were added: (1) 0.5 cc. freshly prepared 0.1% NaNO₂ (Merck, AR). Shake and leave 3 minutes. (2) 0.5 cc. 0.5% ammonium sulfamate (La Motte, pure cryst.). Shake and leave 2 minutes. (3) 0.5 cc. 0.1% *n*(1-naphthyl)-ethylene diamine dihydrochloride (Eastman No. 4835). Shake and leave at least 5 minutes. Keep in the dark until readings are made. It fades somewhat after an hour. The percentage transmission was then determined in the photoelectric colorimeter, and converted to mg. per 100 cc. from standard calibration charts. Recoveries of known added amounts of SNA to tissue aliquots were determined to ascertain the experimental treatments necessarily followed to yield accurate results, varying the boiling time, acid concentration, size of tissue aliquots, and concentration of SNA.

Table 1 illustrates typical results of recoveries of known added amounts of SNA to 80 to 100 mg. rat skin aliquots, using the methods prescribed above.

Many different techniques of washing off excess ointments prior to performing biopsies were tried before it was found best to use soap and warm water, followed by shaving. At least 100 animals were used, and several hundred skin analyses performed, before we

* We wish to acknowledge the assistance of Mr. I. Rusoff, of the Department of Physiological Chemistry, University of Minnesota; and Mr. D. Clausen, of International Milling Company, Minneapolis; who made the determinations on several sulfonamide solutions.

were able to apply an SNA ointment, wash it off immediately and find no skin SNA on analysis of biopsies. The technique described under "Methods" consistently proved satisfactory.

TABLE 1.—RECOVERY OF KNOWN ADDED SULFANILAMIDE FROM RAT ALIQUOTS (80-100 MG. WET WEIGHT)

<i>Mg. Sulfanilamide</i>	
Added	Recovered
0.00	0 00
0 01	0 00995
0 01	0 01
0 02	0 0195
0 02	0 0196
0 03	0 03
0 03	0 0299

Ointment Bases. Seven different ointment bases were arbitrarily selected on the basis of their previous usage. Three were of the oil-in-water emulsion (O/W) type, and 4 of the water-in-oil emulsion type (W/O). The following ointment bases were used:

O/W	A. Sodium lauryl sulfate	1 0
	Stearyl alcohol	10 0
	Cetyl alcohol	3 0
	Spermaceti	10 0
	Glycerol	10 0
	Water	60 0
	B. Liquid petrolatum	57 0
	Peanut oil	3 0
	Triethanolamine	2 0
	Stearic acid	4 0
W/O	Cetyl alcohol	2 S
	Water	71 2
	C. Stearyl alcohol	20 0
	Mineral oil	20 0
	Petrolatum	60 0
	Water	20 0
	1. "Hydrosorb"* (Abbott). A base consisting of oleic acid, white petrolatum, oleic acid ester and amide of diethanolamine.	
	2. Equal parts of white petrolatum and lanolin.	
	3. "Aquaphor"† (Duke). A base consisting of esters of cholesterol mixed with petrolatum.	
	4. Cod-liver oil	20 0
	Lanolin	20 0
	Petrolatum	60 0

* Furnished to us for experimental use by Abbott Laboratories, North Chicago, Ill.

† Furnished to us for experimental use by the Duke Laboratories, Inc., Stamford, Conn.

Sulfanilamide powder was incorporated in 1%, 5% and 10% concentration in each ointment.

Results. The results are summarized in Table 2. Each figure represents averages of at least triplicate determinations (3 skin aliquots) from one piece of skin from each animal for each concentration of SNA, and for each time. The numbers of animals used for each ointment are indicated in the table. A total of 54 animals

were used, representing at least 600 separate analyses. In many cases more than 3 aliquots were taken from each skin biopsy.

TABLE 2.—PENETRATION OF SULFANILAMIDE (SNA) INTO INTACT SKIN OF GUINEA PIGS FROM VARIOUS OINTMENTS

Ointment base	Type of emulsion							
	Oil-in-water			Water-in-oil				
	A	B	C	1	2	3	4	
Number of animals	4	6	4	27	5	4	4	
1% SNA ointment —av. mg. per 100 cc. SNA in skin, after:								
1 day	3.3	4.7	1.8	3.7 ± 1.1	2.3	1.4	1.3	
2 days				8.0 ± 0.8				
3 days	5.3	5.5	3.5	7.8 ± 2.3	3.3	2.3	2.9	
5% SNA ointment —av. mg. per 100 cc. SNA in skin, after:								
1 day	4.7	4.3	3.3	5.2	2.5	2.0	2.4	
3 days	5.9	5.3	4.5	10.4	5.2	3.0	4.3	
10% SNA ointment —av. mg. per 100 cc. SNA in skin, after:								
1 day	4.3 ± 1.5				
2 days	10.3 ± 1.9				
3 days	11.5 ± 2.3				

Scrutiny of Table 2 reveals that SNA penetrates the intact skin more from Base 1 ("Hydrosorb") than from the other bases. Since this base permitted the best penetration of SNA, we chose it for a more exhaustive examination of the effect of time and concentration, as indicated by the number of animals used.⁷ To demonstrate even more strikingly a possible concentration effect, 10% SNA was compared in this base, with 1% for 1, 2 and 3 days.

It is seen that although there is a tendency for increasing concentration of SNA to cause greater skin concentrations, this effect is much less marked and less consistent than the effect of time.

The second conclusion to be drawn from the results is that there is no correlation between the penetration of SNA and the type of ointment base used, at least with respect to whether the emulsion type was oil-in-water or water-in-oil.

There are individual animal differences, and it was for this reason that the large number of animals was used in the case of Base 1, to justify the use of averages. These individual differences are best seen by the probable errors expressed for the results for Base 1, in Table 2.

Discussion. During recent times, many reports have been made of the use of topically applied sulfonamides in the treatment of pyogenic skin infections, infected burns, and so forth. Variable results have been obtained, which have been discussed elsewhere.^{5,6,7} To our knowledge, the present paper presents the first objective study of penetration of a sulfonamide from ointments into skin or tissue. Heretofore workers in this field have selected ointment bases and the concentration of the incorporated sulfonamide purely by personal preference. Our results show clearly that this type of selection is without meaning, at least with respect to SNA and our

special experimental conditions. It would be futile to investigate all the numerous ointment bases which have been recommended and discussed in the medical literature, by the method herein described, since we believe we have shown that there is no logical choice to be made on the basis of present knowledge.

Only a given quantity of SNA is taken up by the skin from the bases within a given time period, and this amount cannot be increased by increasing the concentration in the ointment.

Some preliminary experiments have been performed on intact human skin, using techniques identical to the animal work described above. The results have shown that skin concentrations obtained with corresponding concentrations of SNA in the same bases used are essentially of the same order, justifying in our opinion the extension of the results obtained from animal work to the human.

It is conceivable that an effect of concentration of SNA in an ointment could increase the skin penetration, by more frequent applications. In our work, only one daily application was made.

The human experiments are being extended, and will be reported at a later date, along with the results obtained with other sulfonamides.

Summary. 1. The rate of penetration of sulfanilamide into the intact skin of guinea pigs from 4 typical water-in-oil and 3 oil-in-water emulsion ointment bases has been determined by direct chemical analyses of skin biopsies, with respect to time and concentration of sulfanilamide.

2. A new method of tissue sulfanilamide analysis has been described, which permits large numbers of analyses of total sulfanilamide to be determined in a relatively short time.

3. There is no correlation between the penetration of sulfanilamide and the type of ointment base, at least in regard to whether the base is of the water-in-oil or the oil-in-water emulsion type.

4. Increasing the concentration of sulfanilamide in ointment bases above 1% has little effect on tissue levels of SNA reached.

5. Increasing the time of application of sulfanilamide consistently increased the tissue levels reached.

6. Preliminary human experiments indicate that the results of the animal experiments may be justifiably extended to the human.

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CHOLESTEROL IN THE LUNG AND SERUM OF NORMAL PNEUMONIC RATS

BY ARNOLD WAGNER, M.S., M.D.

AND

J. ROSCOE MILLER, M.S., M.D.

CHICAGO, ILL.

(From the Department of Medicine, Northwestern University Medical School)

It is well known that in certain infections the concentration of cholesterol in the serum undergoes characteristic changes. This has been borne out by the work of Denis³ and Kipp⁵ among the early workers and subsequently by Shope,¹¹ Marino,⁷ McQuarrie and Stoesser,^{8,13} Stoesser,¹⁴ and Steiner and Turner¹² and others. The latter authors generally found that the change in total serum cholesterol concentration is due to variations in the ester fractions, the free fraction remaining fairly constant. Some of the writers and notably Kipp have speculated that the change reflects a mobilization of cholesterol from the blood stream to the site of infection. As the only direct evidence supporting this thought we have the report of Kubota⁶ who states, in a very brief résumé of his work, that in the pneumonic tissue of the rabbit the total cholesterol concentration was "remarkably increased." Suggestive evidence is seen in the work of Christian² who found two distinct types of fat in pneumonic exudations. Indirect evidence suggesting a mobilization of cholesterol in infection appears in the work of Boyd¹ who found an increase of free cholesterol in the leukocytes of the circulating blood during infections, and in the report of Frola⁴ who noted a general diminution in the ester cholesterol of the viscera during the course of experimental peritonitis.

It was the purpose of this experiment to study simultaneously the changing status of free and ester cholesterol in the serum and diseased tissue of rats in which experimental pneumococcus lobar pneumonia has been induced as an anatomically localized, readily accessible infection.

Materials and Method. The experiment was performed upon adult male albino rats supplied from a well-inbred colony and ranging in weight from 180 to 270 gm. The animals were fed the regular stock diet used in this laboratory and received water *ad libitum*.

A Type III pneumococcus culture was supplied by Dr. Francis Gunn, in whose laboratory this strain has served for years in the production of satisfactory rat pneumonias.

Pneumonia was induced in the animals by the technic of Nungester and Jourdonais.⁹

Serum cholesterol determinations were done by the method of Schoenheimer and Sperry.¹⁰ The modification of Sturges and Knudson¹⁵ was employed for the estimation of tissue cholesterol.

Procedure. The rats were inoculated in three groups. At intervals spaced to follow the known course of the disease, groups of animals were

killed. Just prior to killing, several cc. of blood was withdrawn from each by cardiac puncture to supply material for serum cholesterol determination. The entire lobe in which the consolidation appeared was removed for analysis.

Results. *A. Normal Controls.* Serum cholesterol fractions in 26 normal animals are shown in Table 1. The mean value for free cholesterol is seen to be 13.3 mg. per 100 cc., with a standard deviation of ± 2.131 mg. per 100 cc. The mean value for total cholesterol is 49.7 mg. per 100 cc., with a standard deviation of ± 7.36 mg. per 100 cc. The mean free in total ratio is 26.7% with a standard deviation of $\pm 2.61\%$.

TABLE 1.—NORMAL CONCENTRATION OF CHOLESTEROL IN THE SERUM

Rat No	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Free in total %
1	10 6	42 2	25 1
2	14.3	52 2	27.3
3	14 8	57.7	25 7
4	15 5	54 8	28 2
5	15 1	54 9	27 5
6	14 7	58 2	25 3
7	11 0	41 5	26 5
8	10 6	36 6	29 8
9	14 0	49 0	28 6
10	11 0	34 4	32 0
11	13 5	54 0	25 0
12	11 5	49 0	23 5
13	14 1	55 4	25 5
14	14 0	52 0	26 9
15	13 0	46 8	27 8
16	16 4	53 6	30 3
17	12 7	47 3	26.9
18	12 4	49 0	25 3
19	16 0	58 0	27.6
20	19 3	60 4	31 9
21	13 2	57 4	23 0
22	14 1	62 9	22 3
23	11 2	53 3	21 0
24	10 7	43 0	25 0
25	13 6	50 8	26 8
26	10 5	38 6	27 2
Mean	13 3	49 7	26 7
Standard dev.	± 2.131	± 7.36	± 2.61

Tissue cholesterol fractions in 13 normal left lobes are shown in Table 2. Because of the difference in size of the animals the values have not been treated statistically but it is clear that in the range of sizes employed in this experiment the total amount of cholesterol in the left lobe is well in excess of 1 mg. and less than 2 mg. However, the per cent of ester in total cholesterol is independent of the quantity of tissue analyzed and so has been treated statistically. The mean ester/total ratio for 13 left lobes and three groups of right-sided lobes is 5.69%, with a standard deviation of $\pm 1.84\%$.

Tissue cholesterol data are reported as absolute amounts rather than mg. per unit dry weight owing to the fact that technical diffi-

culties in drying the consolidated lobes made the latter figures unreliable.

TABLE 2.—NORMAL CONCENTRATION OF CHOLESTEROL IN THE LEFT LOBE

Rat No.	Free (mg.)	Total (mg.)	Ester in total %
1	1 47	1 59	7 5
2	1 59	1 67	4 8
3	1 72	1 86	7 5
4	1 67	1 81	7 5
5	1 60	1 69	5 7
6	1 83	1 90	4 2
7	1 56	1 62	3 7
8	1 56	1 68	6 8
9	1 69	1 80	5 9
10	1 60	1 78	9 8
11	1 51	1 59	5 4
12	1 83	1 97	6 8
13	1 76	1 86	5 7
Mean	1 64	1 74	

RIGHT LOBES			
A	3 00	3 14	4 6
B	2 94	3 05	3 8
C	3 41	3 60	5 5
Mean			5 69
Standard deviation			±1 84

(Rat A above was a normal animal. Rats B and C had extensive left lobar consolidations and apparently normal right-sided lobes.)

B. Pneumonic Animals. In about half the animals the inoculating catheter slipped into the lobe situated behind the heart rather than the left lobe. This made a considerable difference in the quantity of tissue being analyzed in each case, the former being a much smaller lobe. For this reason the tissue results are reported separately. However, for the general purposes of this experiment it made little difference where the consolidation was located. The sites and estimated extents of the pneumonias which served as material for this report are given in Table 3.

TABLE 3.—SITES AND EXTENTS OF THE CONSOLIDATIONS

Involvement, %	Left lobe	Post-cardiac lobe
100 to 75	4	10
75 to 50	4	4
50 to 25	7	5
Less than 25	2	1

The behavior of the serum cholesterol fractions is shown in Figures 1, 2 and 3. The data are superimposed on the previously established normal means and bands describing ± 3 standard deviations from those means. It is seen that there are no statistically significant changes in either of the fractions despite a clearly expressed tendency toward diminution of the ester fraction (rising free in total ratios) early in the course of the disease, best shown in Figure 3.

The behavior of the tissue cholesterol fractions is shown in Figures 4, 5 and 6. A progressive accumulation of cholesterol is noted from the time of inoculation, with maximum concentrations between the 6th and 9th days. By the 14th day, at which time only a slight discoloration over the area usually occupied by the consolidation remained as evidence of past pneumonia, a return to

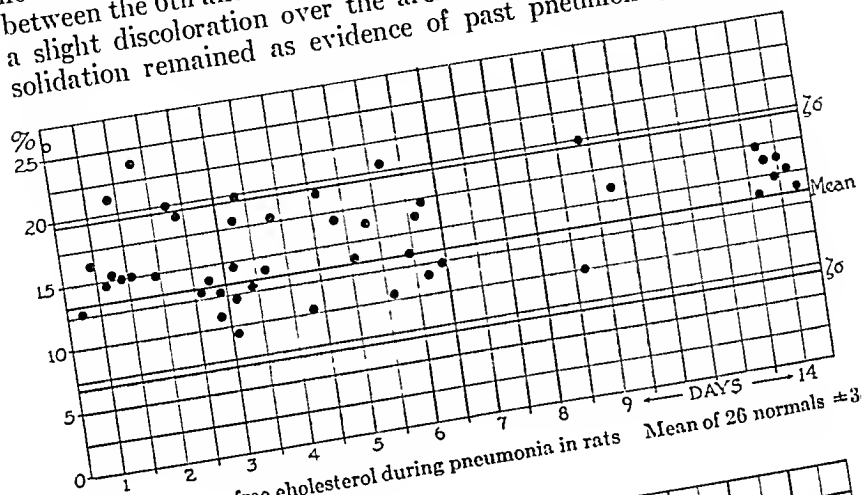


FIG. 1.—Serum-free cholesterol during pneumonia in rats. Mean of 26 normals $\pm 3\sigma$.

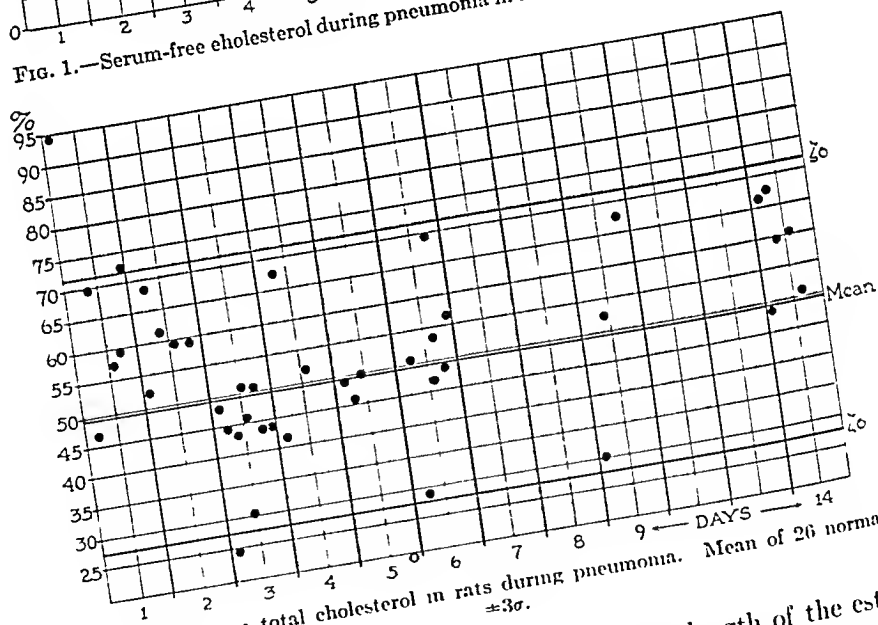


FIG. 2.—Serum total cholesterol in rats during pneumonia. Mean of 26 normals $\pm 3\sigma$.

normal values is seen. The increasing relative length of the ester portion of the lines is noteworthy. This disproportionate increase of esters in the face of rising values for free cholesterol is best shown in Figure 6. Here again the data for ester in total ratios are superimposed upon the normal mean for 13 animals, with ± 3 standard deviations from that mean.

Discussion. In each group of animals some degree of consolidation existed in all subjects and on any given day the age of the lesions was constant, but in no 2 animals was the extent of the consolidation identical. Since the entire lobe was analyzed in each case, it follows that within certain limits the tissue ester in total ratio was affected by "dilution" with variable amounts of normal lung tissue. Such tissue has been shown in Table 2 to contain about 95% cholesterol and 5% esters. While this variation is noteworthy, the total amounts of cholesterol recovered from the pneumonic lungs when compared with the total amounts recovered from the normal lungs make it relatively of less importance.

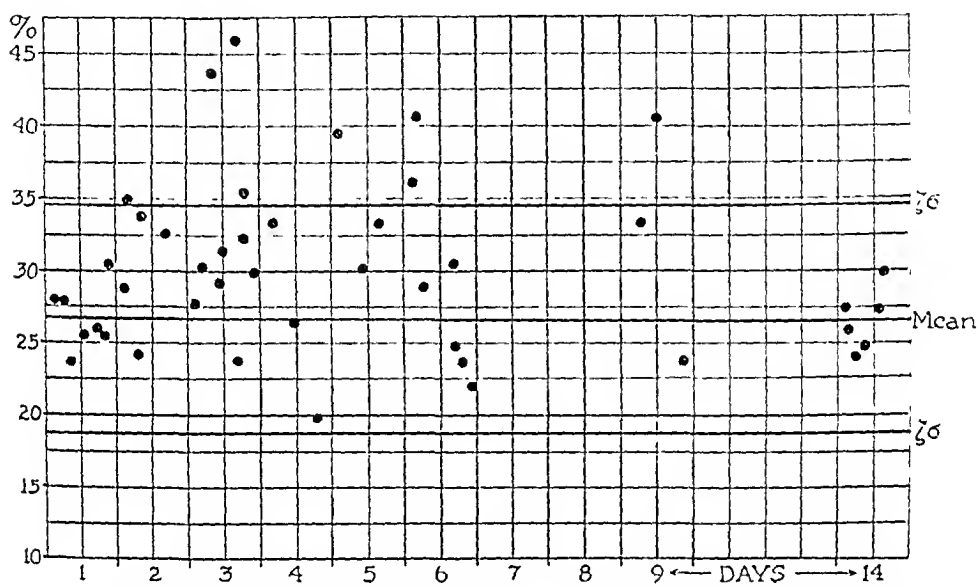
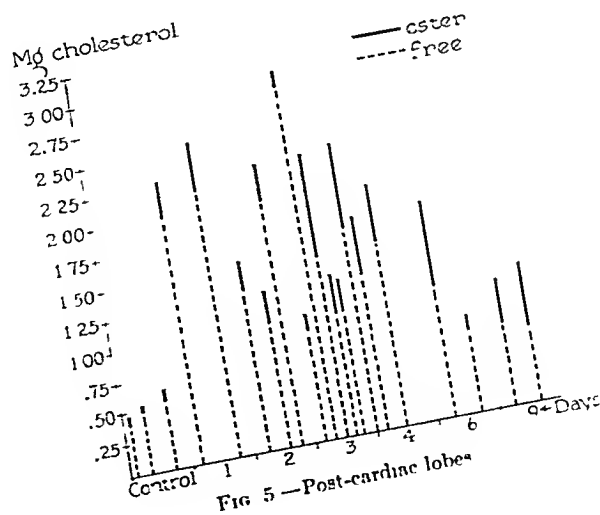
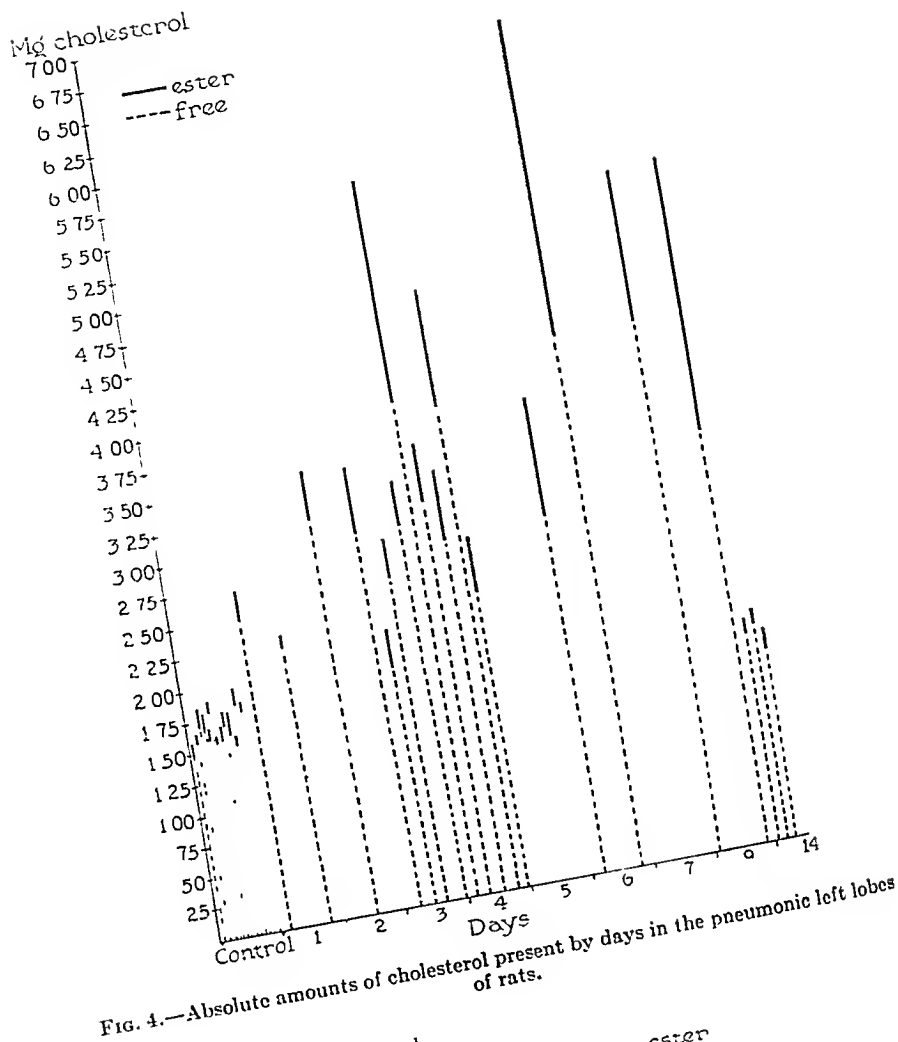


FIG. 3.—Serum-free/total cholesterol ratios during rat pneumonias. Mean of 26 normals $\pm 3\sigma$.

The fact that the serum cholesterol was frequently normal despite extensive accumulations of cholesterol in the lung suggests that the serum is not the ultimate source of the sterol. If involved at all it probably operates as an agent in the transport from tissue depots, and, in certain subjects, maintains a normal serum-free/ester equilibrium in doing so. It is noted that only the lung was analyzed in this study.

As to the origin of the cholesterol that accumulates in the diseased tissues it is probable that multiple sources are involved. The red blood cells, the leukocytes and the serum that find their way into the exudate all are known to contain generous quantities of cholesterol, chiefly in the free state.

There is no present explanation for the daily increase in the ester fraction of the tissue cholesterol. Unless one is to postulate a selective retention of esters from the blood circulating through the con-



solidated area, one must consider the possibility of enzymatic action to explain the progressive apparent esterification. This possibility is the subject of further work currently being done in this laboratory.

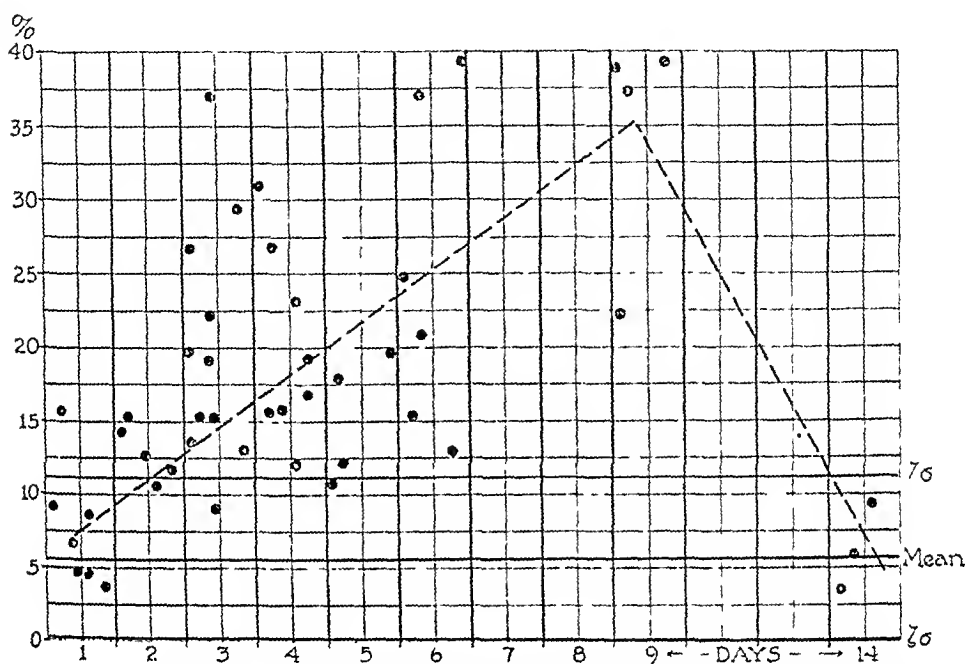


FIG. 6.—Ester/total ratio of cholesterol in pneumonic lobes arranged by days after inoculation (rats).

Summary and Conclusions. Pneumococcus lobar pneumonia was induced in healthy adult albino rats. On specified days after inoculation, groups of the animals were bled from the heart and killed. The sera and diseased lobes were analyzed at once for the cholesterol fractions.

Except for occasional instances early in the course of the disease both free and total cholesterol in the serum remained unchanged.

There was a tendency for the proportion of ester to free cholesterol in the serum to fall. This is expressed as a trend toward increasing free in total ratios early in the course of the disease.

There was a striking absolute increase in the total cholesterol present in the diseased lobe during the course of the pneumonia. This increase involved both free and ester fractions but not in equal or constant degrees.

There was a progressive increase in the proportion of ester cholesterol in the diseased lung during the course of the disease.

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THE EFFECT OF ADRENALINE AND SYMPATHOMIMETIC AMINES UPON TOTAL BODY WATER

By ELDON M. BOYD, M.D.

PROFESSOR OF PHARMACOLOGY, QUEEN'S UNIVERSITY

GRANT M. JOHNSTON, M.D.

RESEARCH ASSISTANT IN PHARMACOLOGY, QUEEN'S UNIVERSITY

AND

BETTY PALMER, B.A.

RESEARCH ASSISTANT IN PHARMACOLOGY, QUEEN'S UNIVERSITY
KINGSTON, CANADA

THERE are few drugs which have been studied more extensively in the pharmacologic laboratory than has adrenaline and yet many phases of its therapeutic action are incompletely understood. One of these is its relief of symptoms in several types of allergic reactions. In recent years, a number of papers have been published in which it has been shown that variations in water metabolism may affect the development of allergic reactions.^{9,12,14,16,17} The suggestion in these and related reports is that changes in water balance do not *cause* allergic reactions but may affect the *susceptibility* of the body to allergens. The hypothesis is succinctly stated by Kern¹² as, "Water and salt retention will favor the development of allergic reactions." While not all agree with Kern's generalization, yet there seemed to be sufficient evidence to warrant a study of the effect of adrenaline and related sympathomimetic amines upon water metabolism.

The most commonly known effect of adrenaline upon body water is its diuretic-antidiuretic reaction originally described by Bardier and Fraenkel in 1899. This reaction has been demonstrated in most vertebrates except the aglomerular fishes¹⁸ and is composed of two reactions, an initial renal vascular reaction of brief duration and secondly a more prolonged effect upon body water-salt metabolism. The initial antidiuretic-diuretic renal vascular reaction is well known and is related to the marked sensitivity of the renal blood-vessels to adrenaline. The second reaction extends over a period of 1 or 2 hours or more, and during it there is a redistribution of

water and salt in the body. The exact changes vary with species of animal, dosage of adrenaline, the state of water balance and other factors. In essence, however, there occurs a loss of water and certain salts from blood and tissues due to an increased output in urine and possibly other channels of excretion.^{2,4,6,8,10,11,13,19,20}

In previous reports, the effect of adrenaline upon water metabolism has been described in terms of its effect upon the rate of urine formation. Changes in total body water do not necessarily parallel changes in the rate of urine formation, and the object of the present investigation was to measure the effect of adrenaline upon total body water. If allergic attacks are associated with retention in tissues of body water, as suggested by Kern¹² and others, then adrenaline might conceivably improve the symptoms if it were to have a dehydrating effect. This latter was found to occur.

The animal selected for this study was the frog because it has a very labile water metabolism. In most higher vertebrates, water conservation is so well developed that it is difficult to demonstrate small effects upon total body water. In the frog, the exchange of body water may be as great as 5% of its body weight per hour.⁵ Several authors have previously reported that adrenaline has no effect upon the total body water of frogs^{1,3,7} but their studies were limited to few animals and a narrow range of doses. As the studies herein reported progressed, it became obvious that a wide range of doses of adrenaline would have to be studied and that large numbers of animals would be needed to bring out the relatively minor and variable dehydrating effect of small doses of the drug.

Leopard frogs, *Rana pipiens*, were used. The animals were acclimatized to room temperature in water overnight, then taken out of water, the urine expressed, the skin carefully dried and body weight determined to the nearest 0.1 gm. on a trip scale balance. Adrenaline hydrochloride in various doses, dispensed in its pharmacopial (B.P.) vehicle, was injected into the dorsal lymph sac. Control animals received the same volume of the vehicle without the adrenaline hydrochloride. The frogs were then placed in 400 ml. beakers covered with weighted glass shields and body weight determined again at hourly intervals. From 25 to 75 frogs were used to find the effect of each dose of adrenaline hydrochloride. The doses studied were from 10^{-25} to 100 mg. per kilo body weight at geometric increments of 10.

Doses of adrenaline hydrochloride less than 10^{-12} mg. per kilo body weight had no effect upon body water. Doses of adrenaline hydrochloride from 10^{-12} to 10^{-5} mg. per kilo had no consistent effect upon body water for 1 hour, but in the second hour they consistently increased the loss of body water by from 20% to 40%. These results are shown in Figure 1, in which the mean difference in the loss of body water in frogs given adrenaline hydrochloride over that in the controls has been expressed as a percentage of the

loss of water in the controls. After the second hour, there again was no consistent effect of adrenaline upon body water.

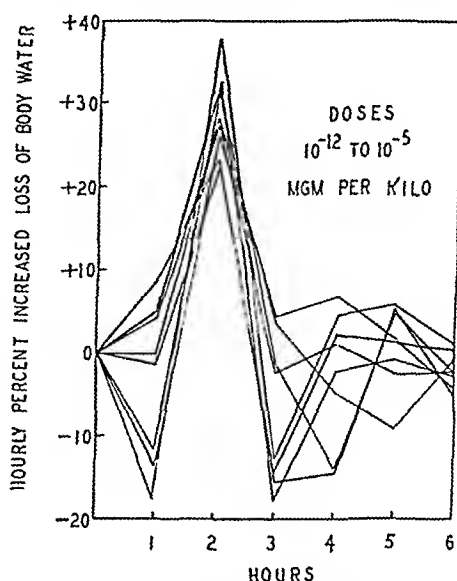


FIG. 1.—The effect of small doses of adrenaline hydrochloride upon the rate of loss of total body water in frogs.

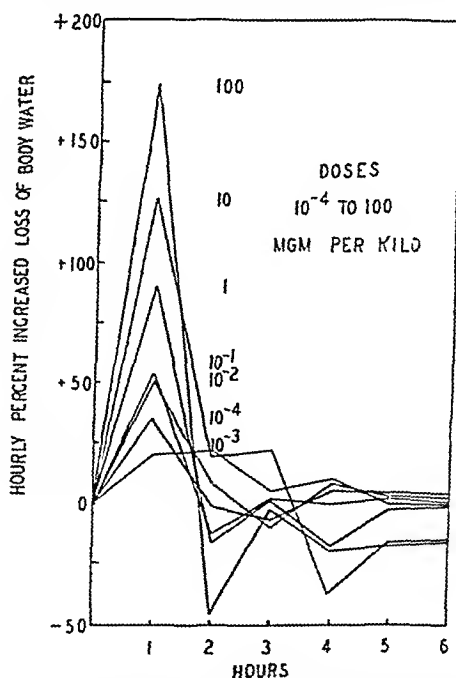


FIG. 2.—The effect of pharmacopeial and larger doses of adrenaline hydrochloride upon the rate of loss of total body water in frogs.

In the larger doses, adrenaline produced an immediate increase in the loss of body water during the first hour after administration as seen in Figure 2. The increase varied from 25% greater than the control value in frogs receiving 10^{-4} and 10^{-3} mg. per kilo body weight of adrenaline hydrochloride, to as much as 175% greater than the control loss of body water in frogs receiving 100 mg. of the drug per kilo. After the first hour, adrenaline had less consistent effects, tending in most groups to have a slight hydrating effect. The recommended pharmacopeial dose of adrenaline hydrochloride corresponds in man to about 10^{-2} or 10^{-3} mg. per kilo subcutaneously, doses which in frogs caused a definite increase in the loss of body water.

These results indicate that adrenaline causes in the frog a stimulation of the loss of body water which may extend over from 1 to 2 hours. The beneficial effect of adrenaline in allergic disorders may perhaps be explained as, in part at least, a stimulation of water loss. The failure of adrenaline therapeutically in certain allergic reactions or allergic-like reactions such as salicylism may be due to such reactions being not necessarily associated with water retention because, of course, water retention is not the only factor concerned in allergic reactions.

Seasonal Variations. Reactions involving shifts in body water often vary with the seasonal shifts in body water. Thus, for example, the Brunn reaction in frogs, which consists of an uptake of body water by frogs kept in water when injected with posterior pituitary extract, disappears almost entirely in the cold winter months in this locality. With this seasonal variation in mind, adrenaline hydrochloride was given at approximately monthly intervals to groups of 30 frogs at varying doses over a period of 1 year. The dehydrating action of adrenaline could be demonstrated and to the same degree with corresponding doses at all seasons of the year.

Ergotoxine Ethanesulphonate. Experiments were next designed to find if ergotoxine ethanesulphonate would inhibit or reverse the dehydrating effect of adrenaline in frogs and the mean results have been charted in Figure 3. Ergotoxine ethanesulphonate alone was injected subcutaneously into a total of 312 frogs in doses of from 10^{-5} to 100 mg. per kilo body weight with the result that there was a consistent retention of body water over a period of 2 hours with all doses, an effect the opposite to that of adrenaline. In a second series of frogs, the animals were given injections of similar doses of ergotoxine ethanesulphonate and then an injection of adrenaline hydrochloride of 1 mg. per kilo body weight. In these latter experiments, the ergotoxine reduced to some extent the dehydrating effect of adrenaline but did not completely inhibit it nor reverse it.

Ergotamine Tartrate. In contrast to the hydrating effect of ergotoxine, ergotamine had no consistent effect upon frog body water in

subcutaneous doses of from 10^{-3} to 10 mg. per kilo body weight. In experiments upon some 300 frogs, there were no significant changes in body water with these doses of ergotamine tartrate which was used in the form of Gynergen, N.N.R. Nor did ergotamine have any effect upon the dehydrating action of adrenaline in experiments arranged as described for ergotoxine.

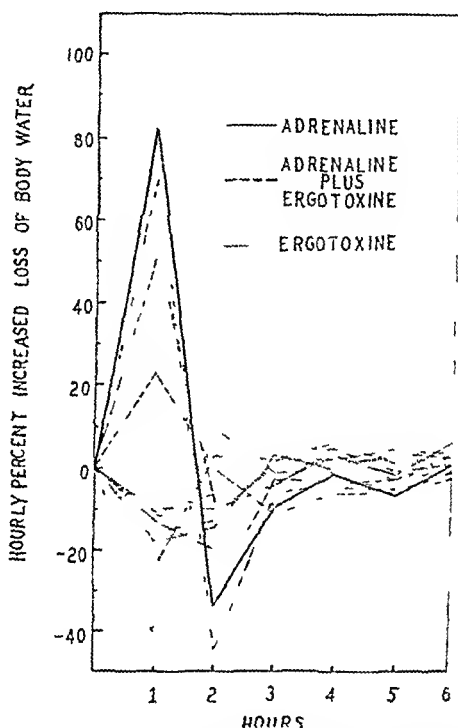


FIG. 3.—The effect of ergotoxine upon the rate of loss of total body water in frogs and upon the dehydrating action of adrenaline hydrochloride.

The difference in the response of frog body water to ergotoxine on the one hand and to ergotamine on the other is of considerable interest pharmacologically because these two alkaloids are almost identical in a qualitative, pharmacologic sense and differ only in a few reactions quantitatively.¹⁵ Clinically, the two drugs are used for almost identical purposes, except in the therapy of migraine where ergotamine is the drug of choice. Migraine is classified by many as an allergic disease and, if Kern's hypothesis is correct, the above findings may indicate at least one reason why ergotamine is used apparently in preference to ergotoxine clinically in migraine. That is, while ergotamine does not dehydrate like adrenaline, it does not hydrate like ergotoxine, which latter would presumably be an advantage in migraine.

Ephedrine Hydrochloride. Ephedrine hydrochloride was given hypodermically to 330 frogs in the same manner as adrenaline hydrochloride and in doses of from 10^{-2} to 100 mg. per kilo body weight. It had no significant effect upon the rate of loss of body water.

Betaphenyl-n-propylamine Hydrochloride. Ephedrine is a derivative of betaphenyl-isopropylamine and adrenaline of betaphenyl-ethylamine. The corresponding n-propylamines have not been studied to the same extent. One of these latter, betaphenyl-n-propylamine hydrochloride was placed at our disposal by Dr. E. Gifford Upjohn of the Upjohn Company with data suggesting that it might be useful in the therapy of bronchial asthma. It was injected into frogs in doses of from 10^{-2} to 100 mg. per kilo body weight in a manner similar to that with adrenaline hydrochloride. In the larger doses of 10 and 100 mg. per kilo, it produced an increased loss of body water which averaged 30% greater than the loss of body water in the controls during the first hour after injection. This effect corresponded to that of adrenaline hydrochloride in doses of about 10^{-3} or 10^{-4} mg. per kilo body weight. In doses of 1 mg. per kilo and less, this n-propylamine had no consistent effect upon body water. The drug was thus similar qualitatively but not quantitatively to adrenaline in its effect upon body water.

Summary. Adrenaline hydrochloride was found to have a dehydrating effect in the frog. Doses of from 10^{-12} to 10^{-5} mg. per kilo body weight speeded up by from 20% to 40% the loss of body water during the second hour after subcutaneous injection. Larger doses up to 100 mg. per kilo body weight increased the loss of body water during the first hour after injection by amounts up to nearly 200% of the water loss of controls.

Ergotoxine ethanesulphonate had the opposite effect, causing a retention of body water for a corresponding period and when given with adrenaline hydrochloride, it decreased to some extent, but did not eliminate or reverse the dehydrating action of adrenaline.

Ergotamine tartrate and ephedrine hydrochloride in corresponding doses had no effect upon frog body water.

Betaphenyl-n-propylamine hydrochloride had a dehydrating effect similar to that of adrenaline hydrochloride but requiring relatively much larger doses to yield a corresponding effect.

The possible relation of these findings to the use of adrenaline in allergic states is discussed.

The authors wish to acknowledge with thanks the coöperation, financial and otherwise, of Mr. C. H. Wilkins of the British Drug Houses (Canada) Limited, of Dr. E. G. Upjohn of the Upjohn Company and of the Wingate Chemical Company of Montreal.

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THE THROMBIC ACTIVITY OF A GLOBULIN FRACTION OF THE PLASMA PROTEINS OF BEEF, SWINE AND HUMAN BLOOD

By MARGARET A. ADAMS, B.A.

LABORATORY ASSISTANT, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL
AND

F. H. L. TAYLOR, Ph.D.

RESEARCH ASSOCIATE IN MEDICINE, HARVARD MEDICAL SCHOOL; CHEMIST, THORNDIKE
MEMORIAL LABORATORY, BOSTON CITY HOSPITAL
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services
[Harvard], Boston City Hospital, and the Department of Medicine,
Harvard Medical School, Boston, Mass.)

PARFENTJEV³ recently published an observation that by a salting-out procedure there could be obtained from rabbit plasma a pseudoglobulin fraction having marked coagulation activity on normal human oxalated blood. We have investigated this pseudoglobulin fraction and have shown that it is thrombic in nature,⁶ can be used as an excellent hemostatic in small wounds² and is effective in decreasing the coagulation time of the circulating blood when administered by mouth in relatively large doses.⁵ The present communication presents evidence that the same material can be obtained from the plasma of human, steer and swine blood.*

Methods. Blood was obtained directly from the jugular veins of steers and collected in an equal volume of 2.5% sodium citrate in 0.9% sodium chloride. The blood was centrifugalized, and the supernatant plasma drawn off. In most instances, a mixture containing equal parts of ether and phenol was added as a preservative, 10 ml. of this preservative being added for each liter of plasma. Human plasma likewise contained this preservative.

* In a letter dated December 29, 1941, Dr. A. G. Hogan of the University of Missouri reported to us that he had obtained, using our methods, an active thrombin preparation having 20 Smith units per mg. of nitrogen from oxalated swine blood.

Two samples of swine plasma were obtained through the courtesy of the Lederle Laboratories. One of these plasmas was prepared by mixing 30% potassium oxalate with blood in the proportion of 1 to 100. The other sample of plasma contained 6% of a 46% solution of sodium citrate as an anticoagulant. No preservative was present in either preparation of swine plasma.

The procedure used was that of Parfentjev³ as standardized in this laboratory⁶ for the preparation of rabbit thrombin. Except where variations were made for reasons discussed below, the beef, human and swine plasmas were precipitated 3 times with 20% ammonium sulphate; the combined filtrates precipitated twice with 30% ammonium sulphate; and the final precipitate dissolved in a small amount of distilled water and dialyzed against running tap water for 48 hours.

After dialysis for 48 hours the contents of the cellophane sacks were filtered to remove the euglobulin precipitate which was always present. The filtrate was adjusted to pH 5.3 with approximately normal lactic acid and the mixture was allowed to stand in the refrigerator overnight. On the following day it was filtered. The precipitate was redissolved in 0.1% sodium chloride and lyophilized in weighed bottles. The filtrate, or portions of it, were usually also lyophilized. When used in quantitative experiments, the dried material was redissolved in sufficient amounts of 0.9% sodium chloride solution to give a concentration of total solids of 12%.

Experimental. In order to study thrombic activity quantitatively, 1:10 or 1:100 dilutions were made from the sodium chloride solutions prepared to contain 12% total solids. Citrated normal human plasma was used as a source of fibrinogen. One milliliter of plasma was pipetted into each of a series of beakers and diluted with 30 ml. of 0.9% sodium chloride solution. Varying amounts of diluted pseudoglobulin preparations were added, and the amount of precipitated fibrin was determined. The fibrinogen content of the plasma was also determined by a modification of Cullen and Van Slyke's method of recalcification.¹

When the standard procedure for preparing rabbit pseudoglobulin was applied to beef plasma without isoelectric precipitation, it was found that the amounts of material required to convert fibrinogen to fibrin in normal human plasma contained much higher nitrogen concentrations than in those experiments in which rabbit pseudoglobulin was used. In order to eliminate the large amount of inactive nitrogenous material apparently present in the beef preparation, two isoelectric precipitations at pH 5.3 were done. Both filtrates and both precipitates were found to possess some thrombic activity. The second precipitation increased the activity only very slightly and decreased the yield of thrombic material considerably. After one isoelectric precipitation a material is obtained which is

usually as potent in promoting blood coagulation as rabbit thrombin without any isoelectric purification.

Table 1 shows a typical comparison of rabbit globulin with beef globulin prepared in the same manner and with beef globulin isoelectrically precipitated at pH 5.3.

TABLE 1 — COMPARISON OF RABBIT GLOBULIN WITH BEEF GLOBULIN

Source of thrombin	Mg thrombin nitrogen added to 1 ml plasma	Mg fibrin precipitated
Rabbit plasma standard procedure	0 01	1 54
	0 02	1 89
	0 03	2 25
Beef plasma standard procedure	0 11	1 10
	0 21	2 40
	0 32	2 22
	0 53	2 50
Beef plasma after isoelectric precipitation	0 007	1 79
	0 01	3 07
	0 07	3 42

Two samples of swine plasma were treated in the same manner as that described for beef plasma, and materials were obtained possessing similar thrombic activity. Table 2 shows a comparison of these two preparations with one made from rabbit plasma.

TABLE 2 — COMPARISON OF RABBIT GLOBULIN WITH SWINE GLOBULIN

Source of thrombin	Mg thrombin nitrogen added to 1 ml plasma	Mg fibrin precipitated
Rabbit plasma standard procedure	0 01	1 91
	0 03	2 61
	0 07	2 77
Oxalated swine plasma after isoelectric precipitation	0 01	1 54
	0 02	2 38
	0 05	2 78
Citrate swine plasma after isoelectric precipitation	0 006	2 76
	0 01	3 57
	0 02	3 73

The pseudoglobulin fraction of Parfentjev was also prepared from human plasma. The pseudoglobulin obtained was thrombic in nature, but the potency of the preparation in relation to precipitation of fibrinogen was much less than similar preparations from rabbits, swine or steer plasma. A typical assay is shown in Table 3.

TABLE 3 — POTENCY OF HUMAN THROMBIN

Source of thrombin	Mg thrombin added to 1 ml plasma	Mg fibrinogen precipitated
Human plasma	0 05	0 63
	0 10	1 30
	0 20	1 54

Parfentjev³ in his original procedure conducted the salting-out at a temperature of 37° C. or at room temperature. Because of the possibility of denaturation of proteins at these temperatures, it seemed of interest to investigate the effects of low temperatures on

the reaction. Therefore, one preparation of beef pseudoglobulin was made at about 4° C. The material obtained possessed thrombic activity similar to that of those beef preparations in which ammonium sulphate precipitation was carried out at 37° C. (Table 4).

The origin of thrombic activity derived from calcium-free plasma remains obscure, but some observations directed at a solution of this problem may be reported at this time.

Since a relationship between blood platelets and blood coagulation has been suggested for many years, an investigation was made of the thrombic activity of pseudoglobulin fractions prepared from beef plasma from which platelets had been removed. Berkefeld filtration and centrifugation were both used as methods of removing platelets. Two preparations were made on beef plasma after it had been passed through a Berkefeld filter. One of these possessed no thrombic activity, and the other was only slightly active (Table 4).

Two samples of beef plasma were then centrifugalized in an angle head centrifuge at 4200 r.p.m. to remove platelets, and the resulting plasma used for preparations of pseudoglobulin. In 1 instance the platelets were reduced from 128,000 to 8000 per c.mm. The final product possessed only slight thrombic activity. The second sample was centrifugalized after the addition of ether-phenol preservative. The platelets in this preparation were reduced from 26,000 to 6000 per c.mm. The final product was one of the most potent preparations made from beef plasma (Table 4).

Recent observations in this laboratory⁴ show that after the addition of certain organic solvents to plasma a globulin may be iso-electrically precipitated which will coagulate oxalated plasma. In consideration of this finding, it seemed possible that ether and phenol used primarily merely as a preservative might actually be important factors in the production of thrombic activity. Moreover, in one experiment cited above, it was observed that plasma made poor in platelets after the addition of phenol and ether was very active, whereas removal of platelets before the addition of these substances apparently decreased the thrombic activity. To further investigate the effects of the ether-phenol preservative, one preparation of beef pseudoglobulin was made from which the preservative was omitted. The resulting material was of only fair potency as shown in Table 4. However, both the preparations made from swine plasma were without preservative of any kind, and both of these were very similar in thrombic activity to the most potent beef pseudoglobulins. As swine plasma was never used in this laboratory with phenol and ether, no comparison can be made for that species.

If calcium ions were present as an impurity during the preparation of the pseudoglobulin fraction, it is conceivable that reaction with the thromboplastin and prothrombin of the plasma might occur resulting in thrombic activity. In order to eliminate calcium ions

from the reaction, one preparation of beef pseudoglobulin was made in which the saline was heavily oxalated at each step of the procedure, as shown in Table 4. The material thus prepared possessed some thrombic activity, but was much less active than those made by the standard procedure.

Table 4 presents the results obtained when preparations made with the variations described above were tested with normal human plasma.

TABLE 4.—VARIATIONS IN PREPARATION OF BEEF PSEUDOGLOBULIN TESTED WITH NORMAL HUMAN PLASMA

Modifications in preparation	Mg. thrombin nitrogen added to 1 ml. plasma	Mg. fibrin precipitated
Beef plasma standard procedure	0 007	2 22
	0 014	2 92
	0 028	3 39
	0 070	3 62
Temperature 4° C.	0 007	0 35
	0 014	2 21
	0 028	2 62
	0 070	2 88
Berkefeld plasma, Experiment I	0 52	2 45
	1 04	2 84
	2 08	3 12
Berkefeld plasma, Experiment II	4 36	0 00
Platelets removed by centrifugation	1 83	1 29
	3 65	1 85
Platelets removed by centrifugation after phenol- ether	0 008	2 00
	0 016	2 69
	0 031	3 06
	0 079	3 15
Ether-phenol omitted	0 11	0 54
	0 21	2 28
	0 53	2 43
Calcium ion excluded	0 13	1 47
	0 26	2 53
	0 65	3 15

Discussion. When beef plasma and swine plasma are used as sources of a globulin fraction possessing thrombic activity, other nitrogen-containing fractions not effective in the coagulation of blood are present in larger amounts than in similar material prepared from rabbit plasma. Therefore, purification by isoelectric precipitation is necessary in order to obtain material possessing thrombic concentration equal to that of rabbit pseudoglobulin.

Apparently it is unnecessary to keep plasma at 37° C. during precipitation with ammonium sulphate. When the procedure was carried out in a refrigerator or in running tap water at about 4° C., the globulin fraction prepared possessed approximately the same amount of thrombic activity as those samples prepared at 37° C. It seems probable that the method could be simplified by carrying it out at room temperature without loss of thrombic activity.

An attempt to investigate the relationship between platelets and the thrombic activity of beef pseudoglobulin indicates that the

platelets may play an important rôle. Table 4 shows that with pseudoglobulin prepared from Berkefeld or centrifuged plasma, nearly 100 times as much "thrombin" nitrogen was required to precipitate fibrin from normal human plasma as was necessary when platelets were present in normal amounts. In fact, one sample of Berkefeld plasma was completely inactive even when the nitrogen content of the pseudoglobulin used was several hundred times as great as that usually required. It is, of course, difficult to determine whether it is the removal of platelets alone by Berkefeld filtration which reduces the potency or whether other necessary factors are also removed.

When phenol and ether were added to plasma before centrifuging to remove platelets, an active clotting globulin was obtained, as shown in Table 4. The explanation of this might be that the platelets had already been affected by the ether and phenol before centrifuging so that the necessary part of the platelets was in solution despite the fact that a count showed very few platelets to be present.

As further evidence of the reaction of ether and phenol, it may be seen from Table 4 that when no preservative was used, more than 10 times the usual amount of "thrombin" nitrogen was required to precipitate fibrin.

In the one experiment in which oxalated saline was used to eliminate calcium ions as a reagent impurity during the preparation, material of reduced thrombic activity was produced. Table 4 shows that roughly 10 times as much nitrogen was needed in the samples of this particular pseudoglobulin preparation as in the standard samples in order to precipitate equal amounts of fibrin.

Summary. 1. Beef plasma and swine plasma may be used as sources of a pseudoglobulin possessing thrombic activity similar to that in rabbit plasma. The beef and swine preparations require more purification in order to obtain activity equal to that derived from rabbit plasma.

2. In the preparation of a beef globulin fraction possessing thrombic activity, the fractionation of proteins with ammonium sulphate may be carried out between 4° and 37° C.

3. The thrombic activity of beef pseudoglobulin is diminished in plasma which has been passed through a Berkefeld filter or made poor in platelets by rapid centrifugalization unless ether and phenol have been added previously to the plasma.

4. Ether and phenol, used originally only as a preservative, appear to play some part in the formation of thrombic activity of beef pseudoglobulin, although potent material has been prepared from swine plasma without this preservative.

5. When oxalate is added to exclude the possible effect of calcium ions on the preparation of beef pseudoglobulin, a material is obtained which possesses diminished thrombic activity.

6. Human plasma when treated by Parfentjev's procedure yields a pseudoglobulin having the properties of thrombin. The two samples of plasma used in this study did not produce as active a product as either rabbit, swine or beef plasma.

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EXPERIMENTAL RIBOFLAVIN DEFICIENCY IN MAN

By JOHN J. BOEHRER, M.D.

ASSISTANT PROFESSOR IN MEDICINE AND PREVENTIVE MEDICINE AND PUBLIC HEALTH,
AND PHYSICIAN, STUDENTS' HEALTH SERVICE

CHARLES E. STANFORD, M.D.

CLINICAL INSTRUCTOR IN OPHTHALMOLOGY AND CONSULTING OPHTHALMOLOGIST,
STUDENTS' HEALTH SERVICE

AND

ELIZABETH RYAN, B.S.

DIETITIAN, STUDENTS' HEALTH SERVICE, UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINN.

FOLLOWING the original descriptions of the syndrome of riboflavin deficiency in man by Sebrell and Butler,⁸ and its experimental duplication by them,⁹ Kruse, Sydenstricker, Sebrell, and Cleckley⁶ demonstrated the occurrence of superficial keratitis in riboflavin deficiency. Their findings were similar in many respects to the ocular changes in riboflavin-deficient animals described by Bessey and Wolbach,¹ and Eckhardt and Johnson.⁴ Further work by the original investigators has served to confirm their earlier observations and has led to their conclusion that "at the present time it seems that superficial vascular keratitis is the earliest and most common visible manifestation of riboflavin deficiency as well as a rather reliable index of early deficiency of the B group of vitamins."⁴

The work of these investigators is of fundamental importance, suggesting as it does a clinical method of some precision in the diagnosis of deficiency disease.

It seemed to us important, therefore, to determine if possible the time relationships in the development of this clinical sign. Accordingly the following experiment was undertaken.

Methods. Since 1939 the Students' Health Service of the University of Minnesota has provided a diet table for the benefit of

those students requiring dietary management for any cause, chiefly obesity, diabetes mellitus, and peptic ulcer. A detailed description of its operation has been published elsewhere.² From the group receiving their meals at this diet table, 6 volunteers, 1 male and 5 females, were chosen for this study. Their status prior to the experimental period may be tabulated as follows:

TABLE 1.—STATUS OF VOLUNTEERS

Name	Sex	Age	Reason for prior dietary treatment	% of standard weight	Duration of prior dietary treatment (days)
L. M.	M	23	Obesity	137	79
M. B.	F	18	Obesity	135	147
F. D.	F	29	Obesity	143	95
E. L.	F	25	Obesity	134	15
J. G.	F	18	Obesity	127	82
J. H.	F	19	Obesity	133	91

All of these individuals had been treated for the periods noted above by a reduction diet calculated to contain the following:

TABLE 2.—COMPOSITION OF REDUCTION DIET

Calories	1013
Protein	70 gm.
Fat	37 gm.
Carbohydrate	100 gm.
Calcium	0.96 gm.
Phosphorus	1.46 gm.
Iron	0.015 gm.
Vitamin A	4500 I.U.
Thiamine	1.6 mg.
Ascorbic acid	80 mg.
Riboflavin	2.1 mg.

Since all of these individuals had demonstrated a satisfactory rate of weight-loss prior to the experimental period, it was hoped that their coöperation in the experimental régime would be good.

These 6 volunteers were divided into 2 groups of 3, designated as "control," and "experimental." All were begun on a diet calculated to contain the following:

TABLE 3.—COMPOSITION OF EXPERIMENTAL LOW RIBOFLAVIN DIET

Calories	1300
Protein	71 gm.
Fat	62.2 gm.
Carbohydrate	160.9 gm.
Vitamin A	4140 I.U.
Thiamine	1.24 mg.
Ascorbic acid	96 mg.
Riboflavin	471 µg.

Three daily menus were used in rotation. These are listed in Table 4.

All riboflavin values of foods were taken from the tables of Bowes and Church.³

TABLE 4.—MENUS OF EXPERIMENTAL LOW RIBOFLAVIN DIET

Day 1		Day 2		Day 3	
1300 Calories		1300 Calories		1300 Calories	
Riboflavin (μg.)		Riboflavin (μg.)		Riboflavin (μg.)	
BREAKFAST:		BREAKFAST:		BREAKFAST:	
3 oz. grapejuice + 4 tbsp. gelatin	9	3 oz. pineapple juice + 4 tbsp. gelatin	18	3 oz. grapefruit juice + 4 tbsp. gelatin	18
Applesauce	33	Tangerine	25	Sliced banana	10
White bread (not enriched)	15	Bacon (3 str.)	15	Bacon (3 str.)	15
Butter (½ pat)	1	White bread	15	White bread	15
Bacon (fried—3 str.)	15	Butter (½ pat)	1	Butter (½ pat)	1
Coffee	—	Coffee	—	Coffee	—
	73		74		59
LUNCH:		LUNCH:		LUNCH:	
Spaghetti and tomatoes	36	Vegetable soup	55	Rice with tomatoes	35
with 25 gm. ground meat	20	1 oz. boiled ham (sandwich)	35	3 str. bacon	15
Grapefruit section salad	35	2 white bread (thin) (cut crust)	30	50 raw carrot strips	10
with 1 inner leaf lettuce	4	Butter (½ pat)	—	White bread	15
White bread (not enriched)	15	lettuce leaf	5	Butter (½ pat)	1
Butter (½ pat)	1	Baked apple	30	Red apple	30
Crushed pineapple	25	Tea or coffee	—	Coffee or tea	—
Tea or coffee	—		155		106
	136				
DINNER:		DINNER:		DINNER:	
Beef tenderloin	130	Beef roast	130	Cured ham (75 gm.)	150
Carrots	20	Asparagus (canned)	35	Baked or boiled potato	40
Small boiled potato	40	Small baked potato	40	Stewed tomatoes	45
50 gm. tomato salad	20	50 gm. lettuce salad (inner leaves)	20	Celery salad (50 gm. with inner lettuce leaf)	27
with 1 inner leaf lettuce	4	White roll	15	½ white bread	15
½ white bread (not enriched)	15	Butter (½ pat)	1	Butter (½ pat)	1
Butter (½ pat)	1	½ grapefruit	35	Canned blueberries	15
Sliced banana	10	Coffee or tea	—	Coffee or tea	—
Coffee or tea	—		276		283
	240				
Total micrograms riboflavin, 449		Total micrograms riboflavin, 505		Total micrograms riboflavin, 458	

In addition to this diet, all 6 received daily vitamin and mineral supplements as follows:

TABLE 5.—VITAMIN AND MINERAL SUPPLEMENTS

Calcium	1 gm.
Phosphorus	1 gm.
Iron2 gm.
Nicotinic acid	50 mg.
Calcium panthothenate	2 mg.
Pyridoxine	2 mg.

In addition to these, the control group received without their knowledge a daily supplement of 3 mg. of riboflavin. Two of us (J.J.B. and C.E.S.) who followed the physical status of these volunteers throughout the experiment, were unaware of the identities of the individuals in the control and experimental groups until the end of the experiment.

Each volunteer was requested to report for slitlamp study at the beginning of the period, and twice a week thereafter. (Later once a week.)

Because of the exigencies of the school year, this experiment had to be terminated, unfortunately, after only 5 weeks of observation.

Results. *Experimental Group.*

1. *M.B.* Developed aphthous stomatitis 21st-28th days. No objective evidence of glossitis. No diffuse soreness of mouth or tongue. No eye symptoms at any time. Stated that the diet was very unpleasant, and admitted extra-food intake on numerous occasions. Gained 5 pounds.

Slitlamp findings:

Day 1: Negative. Day 7: Negative. Day 15: Negative. Day 22: Slight fullness of vessels in upper nasal quadrants. Day 29: No change. Conclusion: No abnormalities demonstrated.

2. *E.L.* Developed aphthous stomatitis 35th day. No diffuse soreness of mouth or tongue; no objective manifestations of glossitis. On 14th day developed photophobia which persisted until resumption of normal diet. Weight loss $8\frac{1}{2}$ poynds.

Slitlamp findings:

Day 1: Negative. Day 6: Negative. Day 13: Possibly slight increase in amount of blood in limbal plexus. Day 20: No change. Day 27: No change. Day 35: No change. Conclusion: No abnormalities demonstrated.

3. *J.H.* Complained of unusual fatigue beginning on 8th day. Disappeared 6 days after resumption of normal diet. No eye symptoms at any time. No glossitis. Weight gain 4 pounds.

Slitlamp findings:

Day 1: Negative. Day 5: Negative. Day 10: Negative. Day 15: Negative. Day 22: Negative. Day 29: Negative. Conclusion: No abnormalities demonstrated.

Control Group.

1. *L.M.* Complained of visual fatigue after 7th day. Also noted general fatigue after 7th day. Weight loss 12 pounds.

Slitlamp findings:

Day 1: Negative. Day 8: Negative. Day 15: Negative. Day 22: Few streamers off nasal limbus, left eye. Day 29: Additional fine capillary extension from nasal limbus, both eyes. No secondary capillary loops.

(On Day 30 L.M. resumed a "normal" diet.)

Day 51: No change.

(On Day 52 L.M. was given 9 mg. of riboflavin a day in addition to his "normal" diet.)

Day 65: No change. Riboflavin discontinued.

Day 105: No change. Fine capillary streamers still present. Still complains of occasional eye fatigue. (No uncorrected refractive error.) Weight gain of 8 pounds since discontinuance of experimental diet. Conclusion: Minimal, but definite abnormality demonstrated.

2. *F.D.* No symptoms of any kind. Weight loss 2 pounds.

Slitlamp findings:

Day 1: Negative. Day 5: Negative. Day 12: Negative. Day 19: Negative. Day 26: Negative. Conclusion: No abnormalities demonstrated.

3. *J.G.* Sore tongue from 21st to 25th day. No objective signs. No visual symptoms. Weight loss 1 pound.

Slitlamp findings:

Day 1: Negative. Day 5: Negative. Day 17: Negative. Day 24: Negative. Day 31: Negative. Conclusion: No abnormalities demonstrated.

Comment. The failure of our experimental subjects to develop corneal vascularization is not in accordance with the statement of Sydenstricker, Kelly, and Weaver,¹³ who state, "Under experimental conditions, within a few days, often only two, empty capillaries can be seen arising from the apices of the loops outlining the scleral projections . . . in 2 or 3 days more they form complete loops through which red cells circulate irregularly and in clumps." Their experimental conditions were not cited. We are not prepared at present to say that this lack of agreement is of any significance. The conditions of our experiment did not permit us to be certain of the coöperation of our subjects. Further, we have no objective evidence (*i. e.*, diminished urinary excretion of riboflavin) that our subjects were actually deficient in riboflavin. It may be that a longer period of deprivation is necessary to bring an individual on a previously adequate intake of riboflavin to the point where objective signs are manifest. Repetition of this experiment with coincident determination of urinary riboflavin is obviously indicated, and will be initiated in the near future.

The significant point, it seems to us, which emerges from this study is the fact that definite evidence of corneal vascularization occurred in one of the subjects of the *control* group, in spite of an intake of riboflavin of approximately 3.5 mg. per day, whereas an intake of approximately 2.1 mg. of riboflavin per day for 79 days previously, while on the reduction diet, had not resulted in keratitis. This previous period would seem to eliminate defective absorption or defective phosphorylation of riboflavin as etiologic factors in the keratitis.

Further, a "normal" (non-reduction) diet for 3 weeks following the experimental period failed to alter the keratitis, as did the administration of 9 mg. of riboflavin a day for 14 additional days. Theoretically, there are several possibilities which might account for the appearance and persistence of keratitis in a patient whose intake of riboflavin conformed to present ideas of adequate riboflavin supply, and which was greater than a previous known intake of riboflavin.

Summary and Conclusions. 1. Superficial keratitis, like cheilosis,⁷ may be found to be a relatively non-specific response to vitamin deficiency.

2. Lack of "balance" in vitamin intake may cause riboflavin deficiency, even with a relatively high intake of riboflavin. Sydenstricker,¹¹ and Spies, Stanberry, Williams, Jukes, and Babcock¹⁰ have emphasized the rôles of pyridoxine and pantothenic acid, respectively, in the mobilization and utilization of riboflavin. Unfortunately, presently available food analyses are not complete enough to permit us to compare pyridoxine and pantothenic acid intakes of our reduction and experimental diets.

3. It may be that riboflavin *plus* other dietary factors are required

to prevent keratitis. In this connection it may be recalled that Johnson and Eckhardt have already suggested that "factors additional to riboflavin are concerned with the healthy state of the cornea".⁵ And Sydenstricker, Sebrell, Cleckley, and Kruse¹⁴ stated: "It seems possible that other conditioning factors as yet undetermined, may be potent in the production of ariboflavinosis."

4. The keratitis in case L.M. may have been coincident, and unrelated to vitamin deficiency. This is supported by its failure to subside after large doses of riboflavin, plus a "normal" diet.

5. Superficial keratitis, of the type described as specific for riboflavin deficiency, appeared in a patient on a known and theoretically optimal intake of riboflavin. This failed to disappear on a "normal" diet, plus additional riboflavin.

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FOCAL NECROSIS OF THE ADRENAL CORTEX

By NATHAN MITCHELL, M.D.

ASSISTANT PATHOLOGIST

AND

ALFRED ANGRIST, M.D.

PATHOLOGIST

JAMAICA, LONG ISLAND, N. Y.

(From the Pathology Department, Queens General Hospital)

IN reviewing the literature on focal necrosis of the adrenal cortex, it is seen that a wide variety of etiologic factors are implicated. Moschcowitz¹ reported 2 cases, and offered a résumé of pathologic and experimental observations. One of his cases was a 41 year old male who died of uremia complicating calculous disease of the kidneys. He observed more than a dozen foci of necrosis in the adrenal cortex, with intense surrounding polymuclear reaction.

The periadrenal tissue was hemorrhagic with thrombosis of the veins. The second case was that of an 8 year old girl with chronic glomerulonephritis. Multiple focal necrosis with polynuclear reaction were seen, in addition to bacterial emboli in the regional vessels. The relationship of the bacterial emboli to the foci of necrosis is open to question. His illustrations show a notable absence of reaction about some of the bacteria-filled vessels, and the presumption remains that postmortem bacterial proliferation may be represented. His conclusions took cognizance of this, for he inferred that adrenal cortical necrosis may result from either vascular or "toxic" effects. Moschcowitz quoted many authors, including Ziegler, Aschoff, Neusser and Wiesel, Loper and Oppenheim, and Roux and Yersin, all of whom stressed the rôle of infectious diseases in the causation of focal necrosis of the adrenal cortex. Diphtheria was associated with the necrotic lesions most often, but similar lesions were noted in cases of variola, typhoid and tetanus. Experimentally induced lesions were noted particularly with diphtheria toxin. However, identical changes were produced with *B. tetani*, *B. anthracis*, and the pneumococcus. McLaughlin noted the common association of focal necrosis of the adrenal cortex and Curling ulcers of the duodenum in cases of fatal burns. He quoted Weiskotten, who reported 6 cases of fatal burns showing hemorrhage and necrosis of the adrenal. McLaughlin inferred a definite bearing of the adrenal necrosis upon the causation of the Curling ulcers and succeeded in producing ulcerations of the duodenum and elsewhere by experimental destruction of the adrenal.

Hass² reported a case of a premature infant with multiple areas of focal necrosis with inflammatory reaction in the liver and adrenal. He noted acidophilic and basophilic intranuclear inclusion bodies in the parenchymal cells and suggested a virus etiology. Grollman¹ summarizes the subject of focal necrosis by the following statement: "In acute bacterial toxemias, focal necrosis are often seen in the *zona faciculata* which resemble those occurring in the spleen and other viscera." Oestern⁵ reported a case of miliary necrosis in the lung and adrenal in a premature infant who died on the second day of life. He noted the resemblance of the necrotic foci to tubercles, and described a polynuclear inflammatory reaction. In arriving at a conclusion as to the etiology of the necrosis, Oestern quoted the work of several authors including Kaufmann, Amsler, Schneider, Schwartz, and Konschegg. Most of these writers stressed focal necrosis of the liver in infants in their discussion of etiology. Plump "U" or "S" shaped rods stained by the Levaditi method, and not by Gram stain; Gram-positive rods resembling diphtheroids; and complete absence of bacterial agents were reported by different authors. Oestern, Kaufmann, and Amsler were uncertain of the etiologic agent, but suggested "intestinal intoxication" as a possible mechanism.

Case	Age	Sex	TABLE 1.	
			Cause of death	Hypertensive heart dis.
1	64	F		
2	63			

Case	Sex	Age	Local disease	General disease process	Endocrine disturbances	Associated pathologic changes
2	M	63	Pulmonary embolus			Thrombosis of pulmonary arteries with infarction of lung; thrombosis of veins of thorax and pampiniform plexus of Thrombophlebitis of right thigh
3	F	33	Meningococcus meningitis			Thrombosis of cerebral veins
4	F	62	Lobar pneumonia			
5	F	54	Generalized peritonitis			
6	F	63		Fibrinous pericarditis Meningitis Pneumonia Peritonitis (strep. non-hem.)	Diabetes mellitus	
7	M	25		Terminal sepsis (<i>B. coli</i>)	Diabetes mellitus	Carcinoma of cervix with ulceration and fistula formation to peritoneum, ulcerative colitis and proctitis (post-radiation); Carcinoma of pulmonary vessels jaundice, miniature abscesses of kidney; furetion
8	M	23	Generalized peritonitis; sepsis	Peritonitis (<i>B. coli</i>) (strep. non-hem.)		Suppurative appendicitis
9	M	54	Diabetic coma			
10	M	56	Hodgkin's disease			
11	F	48	Neuroblastoma			
12	F	44	Cerebral hemorrhage	Terminal sepsis Lobar pneumonia (pneu. Type XVI)	Diabetes mellitus	
13	F	84	Uremia		Diabetes mellitus; basophilic adenoma of pituitary	Miniature abscesses of liver and spleen Metastasis in adrenal
14	F	14 mo.	Coronary thrombosis; myocardial infarction		Eosinophilic adenoma of pituitary	Cushing's syndrome, obesity, hirsutism, hypertension, diabetes
15	F	68	Massive bronchopneumonia	Lobular pneumonia Bronchopneumonia	Diabetes mellitus	Malignant nephrosclerosis; hyperplasia of parathyroids; dissecting aneurysm of aorta; pancreatic fibrosis
16	F	75	Bronchopneumonia			Congenital stenosis of duodenum with intestinal obstruction; dilatation of pancreatic ducts; chronic intestinal pan-ileum with infarction; leukoplakia of esophagus
17	M	35	Multiple peritoneal abscesses	Bronchopneumonia; membranous cystitis; pelvic peritonitis		Pernicious anemia?
18	F	76	Brain abscess	Peritoneal abscesses; bronchopneumonia		
			Shock, multiple fractures	Brain abscess; meningitis (strep. hem.)		
						Thrombosis of left uterine vein; thrombosis of splenic artery; cachexia Multiple recent peptic ulcers; traumatic softening of pituitary (operative) Multiple fractures; acute ulceration of jejunum

The 18 cases of focal necrosis of the adrenal cortex listed below in Table 1 represent lesions discovered incidentally during the routine 3080 autopsies at the Queens General Hospital in the first 6 years of its existence. With the exception of Case 16, all lesions were seen microscopically in the single section of the adrenal gland taken in all autopsies. In Table 1 are listed all relevant associated clinical and pathologic findings. During the course of the analysis of these cases, the presence of other factors such as blood sugar and urea levels, blood pressure, and focal necrosis in other viscera was noted. Since there was no correlation of these factors with the finding of adrenal necrosis, they are not listed. All lesions were studied on formalin fixed, paraffin imbedded material stained with hematoxylin and eosin. Giemsa and Gram stains were done on lesions showing recent changes.

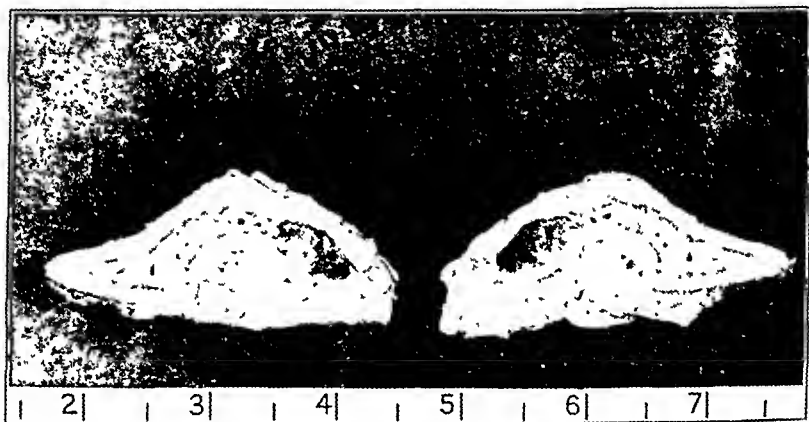


FIG. 1.—Case 16. Oval dark brown nodular cytonecrotic mass in reticularis zone. ($\times 2.5$.)

Age and Sex. Eleven females and 6 males comprise the series. The ages range from 14 months to 84 years, with a mean age of 50 years.

Pathologic Features. The single gross lesion measured 8 by 2 mm. (Fig. 1). It appeared as an elliptical, translucent, brownish mass situated in the reticularis layer, and was raised slightly above the surface of the adjacent parenchyma.

The histologic features are outlined in Table 2. The lesions were of recent origin in 12 instances and showed evidence of chronicity in 5. The acute changes were of 2 types. The first consisted of a focal coagulation necrosis of the adrenal cortical tissue. The size of such areas varied greatly, ranging from 25μ to 2340μ . They were encountered mainly in the *zona fasciculata*, but were also seen in the other 2 layers and in one instance reached to the capsule (Fig. 2). Some of the zones of necrosis bore a distinct resemblance to tubercle

structures. Complete autopsy examination in these cases failed to reveal any active or inactive tuberculosis and stains for acid-fast bacilli were negative. In Case 1, the necrotic focus simulated a miniature caseous tubercle, while in Case 17 a central area of coagulation necrosis was surrounded by a ring of lymphocytic cells and a single Langhans giant cell. The giant cell may have been of the foreign body type (Fig. 3), reactive to the liberation of lipid material in the region of the necrotic focus, though fusion of altered cortical epithelium is suggested by cytology and staining properties.

TABLE 2.—RÉSUMÉ OF HISTOPATHOLOGIC FINDINGS

Case No.	Size in μ	Location	Histopathologic features
1	195	Fasciculata	Focal coagulation necrosis; resemblance to caseous tubercle; multiple foci (3)
2	?	Reticularis	Numerous areas of rounded calcification and fibrosis along reticularis with no reaction
3	520	Glomerulosa and outer fasciculata	Focal collagenous scarring; rather thin remaining glomerulosa
4	390	Fasciculata (inner)	Focal coagulation necrosis with atrophy of adjacent cells and some brownish pigmentation
5	156	Fasciculata (inner)	Focal coagulation necrosis of group of cells; little inflammatory reaction
6	25 to ?	Reticularis, fasciculata	Multiple focal rounded and linear areas of cytonecrosis with and without pigmentation
7	1500	All 3 layers	Focal coagulation necrosis with marked inflammatory reaction, polynuclear cells predominating; adjacent atrophic degenerated cortical cells
8	?	Reticularis	Multiple focal areas of calcification in rounded globules; wide triangular zone of fibrosis adjacent to medulla
9	780	Fasciculata (mid-zone)	Focal coagulation necrosis with vacuolization of regional cortical cells; preservation of sinusoidal and endothelial structures
10	150	Fasciculata	Focal coagulation necrosis with included fibrinoid material with surrounding acute inflammatory reaction
11	260	Fasciculata (upper)	Localized rounded fibrotic zone with some hyalinosis and ossification
12	400	Reticularis (inner)	Rounded zone of fibrosis
13	2340	Fasciculata, glomerulosa and capsule	Focal coagulation necrosis without atrophy of cells; marked regional inflammatory reaction and adjacent zone of liposis
14	450	All 3 layers	Multiple areas of focal coagulation necrosis with regional polynuclear reaction
15	580	Interrenal tissue	Centrally placed extensive coagulation necrosis without inflammatory reaction; no change in adrenal
16	8 x 2 mm.	Reticularis	Pigmented degenerated and atrophic necrotic cells in nodular adenomatoid area
17	720	Glomerulosa, fasciculata	Focal coagulation necrosis with distinct tubercle-like structure, regional Langhans type giant cell and considerable round cell infiltration locally and in medulla
18	50-70	Fasciculata	Multiple with both focal coagulative zones and zones with marked involutional atrophic changes

In the center of one of the foci of coagulation necrosis (Case 10), fibrinoid material was identified. The amount of inflammatory reaction around the areas of coagulation necrosis varied greatly, and was usually polynuclear in character. In Case 15, in which the necrosis occurred in an island of interrenal cortical tissue, no inflammatory cells could be seen (Fig. 4). In Case 14, the marked polynuclear exudation approached the reaction seen in suppurative inflammation (Fig. 5). Hemorrhage in the necrotic foci was an inconstant feature, but was definite in some cases and is of theoretical interest. Although the basic structure of the adrenal cortex was destroyed in most of the necrotic foci, distinct preservation of



FIG. 2. Case 13. Area of coagulation necrosis with surrounding polynuclear reaction adjacent to zone of liposis. Extension of inflammatory exudate to region of capsule seen at upper right. ($\times 175$.)

sinusoidal reticulum and endothelium was seen in Case 7 (Fig. 6). This type of coagulation necrosis was sharply delimited without transition to regional cortex.

The other type of acute change was one of localized cytoncrosis of a varying number of individual cortical cells (Fig. 7). The nuclei of the cells were for the most part pyknotic, but occasionally could not be seen at all. The size of such cells was almost invariably smaller than usual. The cytoplasm was coarsely granular and often contained abundant brownish pigment which made the entire necrotic focus stand out in sharp contrast against the regional normal parenchyma. It was this feature which undoubtedly accounted for the ease with which the gross lesion shown in Figure 1

made itself evident. The necrotic pigmented cells often appeared shrunk and separated from the basement membrane. This type of focus showed greater tendency to transition to regional cortical epithelium with degenerative changes in adjacent cells. No thrombosis was found in the smaller or larger vessels of the tissue adjacent to any necrotic zones.



FIG. 3.—Case 17. Langhans type of giant cell and round cell infiltration adjacent to area of coagulation necrosis resembling caseous tubercle beyond upper border of photograph. ($\times 750$.)

Numerous stages in the organization and eventual fate of the necrotic foci were observed. One early phase of the organization process was seen in Case 12. A well-rounded zone was seen in which the center was composed of finely fibrillar collagenous tissue, with small round inflammatory cells and somewhat dilated capillary channels containing red blood cells (Fig. 8). In Case 3, more coarsely fibrillar collagenous tissue was seen with included fibroblastic cells and no inflammatory cells (Fig. 9). The scar tissue in this instance extended into the regional cortex and capsule in an

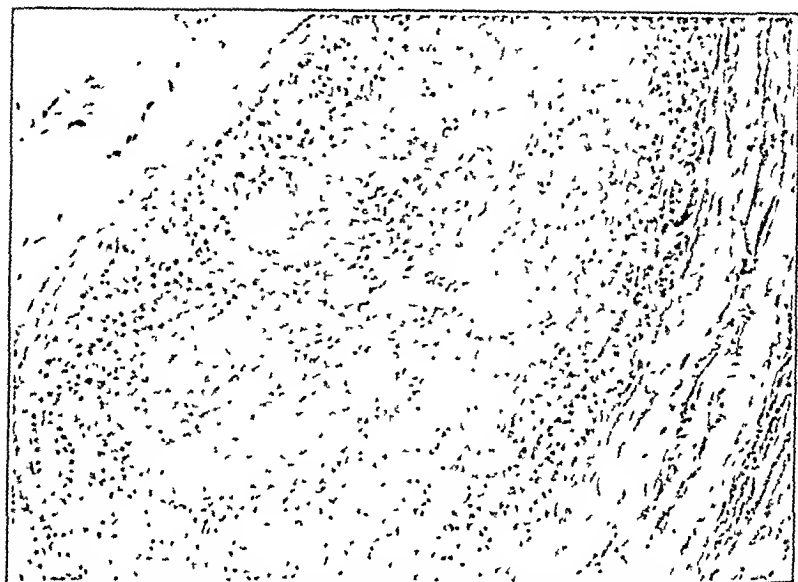


FIG. 4—Case 15 Interrenal tissue showing extensive central coagulation necrosis with peripheral rim of intact cortical tissue. Note pyknotic nuclear remnants in left lower portion. Capsule of adrenal seen at lower right margin ($\times 175$)

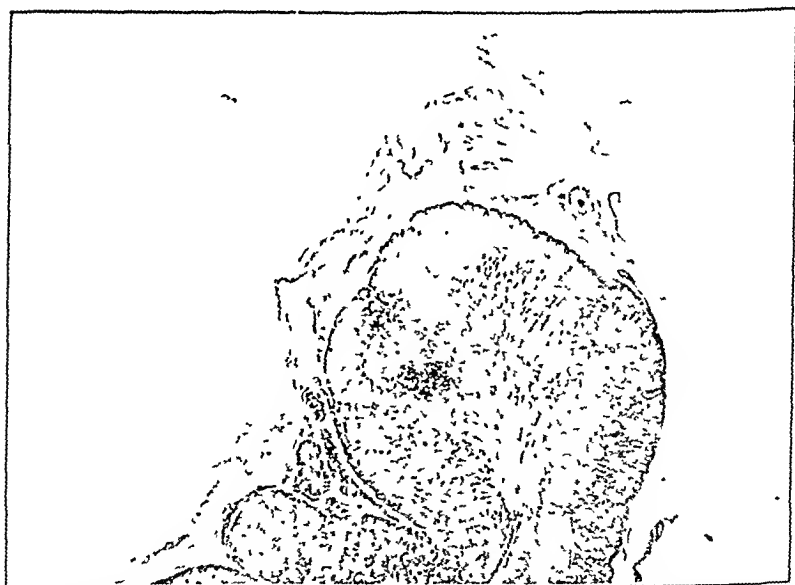


FIG. 5—Case 14 One of several rounded foci of coagulation necrosis with marked polynuclear reaction at periphery in a 14 month old infant with remnant of organized atrophic centrally placed androgenic zone ($\times 24$)

irregular manner. Diffuse and focal calcification of groups of cortical cell remnants both within and separated from large fibrotic areas was also noted in Cases 2 and 8. In Case 11, a rounded hyalinized fibrotic zone was present, with a central area of ossification and early marrow formation (Fig. 10).

Discussion. In the literature, focal necrosis of the adrenal has been associated with actual infection or "toxic" states. Eleven of our 12 cases showing recent changes had some infectious disease



FIG. 6.—Case 7. Zone of coagulation necrosis of cortical cells with preservation of reticular structure and adjacent polynuclear reaction. ($\times 175$.)

process, varying from limited lobular pneumonia to extensive suppurative peritonitis. It is our impression that endocrine abnormalities do contribute in some measure to the evolution of focal necrosis. Diabetes mellitus was noted in 5 of the cases, and it is important to note further that no infectious process was present in 2 of them. In one of the latter, Cushing's syndrome was fully developed, and the diagnosis of basophilic adenoma of the pituitary was confirmed at autopsy. In the other instance, an eosinophilic

adenoma of the pituitary was noted as an incidental finding in a case of malignant nephrosclerosis with uremia. Two of the cases included above with the infectious processes, showed cachexia. Arterial and venous thrombosis in widely divergent locations outside of the adrenal was noted in 6 cases. In only one instance, a case of hypertensive heart disease, neither an infectious process nor an endocrine problem was present.

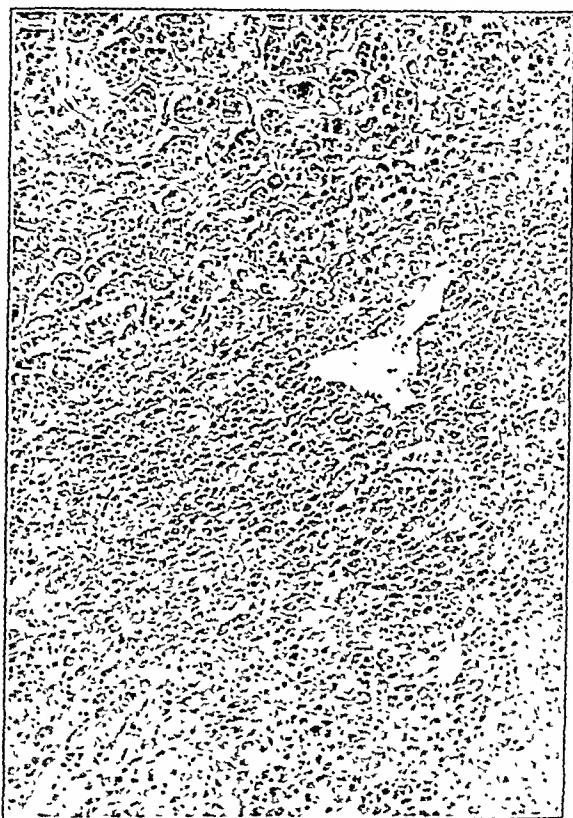


FIG. 7.—Case 16. Microscopic section corresponding to gross lesion seen in Figure 1. Edge of large zone of cytonecrosis. ($\times 175$.)

The multiplicity of factors observed above favors the consideration that focal adrenal cortical necrosis is not a specific disease entity with a single etiology, and tends to implicate a physiologic component in the reaction.

The possibility does remain that absorption of many necrotic zones occur. In the cases where the reticulum remains preserved, the preëxisting events of degeneration and necrosis may be completely lost to observation by regeneration of persistent cortical cells. The physiologic sequence of events is then approached.

With absorption, fatty replacement by large fat cells may produce the phenomenon of liposis occasionally seen in the adrenal cortex (Fig. 1).

The relationship of "exhaustion lipoidosis" of the fasciculata and the exaggerated physiologic involutional and degenerative changes in the reticularis zone, to the focal degenerative and necrotic foci described, is yet to be established. In the fully formed adrenal, the reticularis represents the final zone of degeneration and involu-

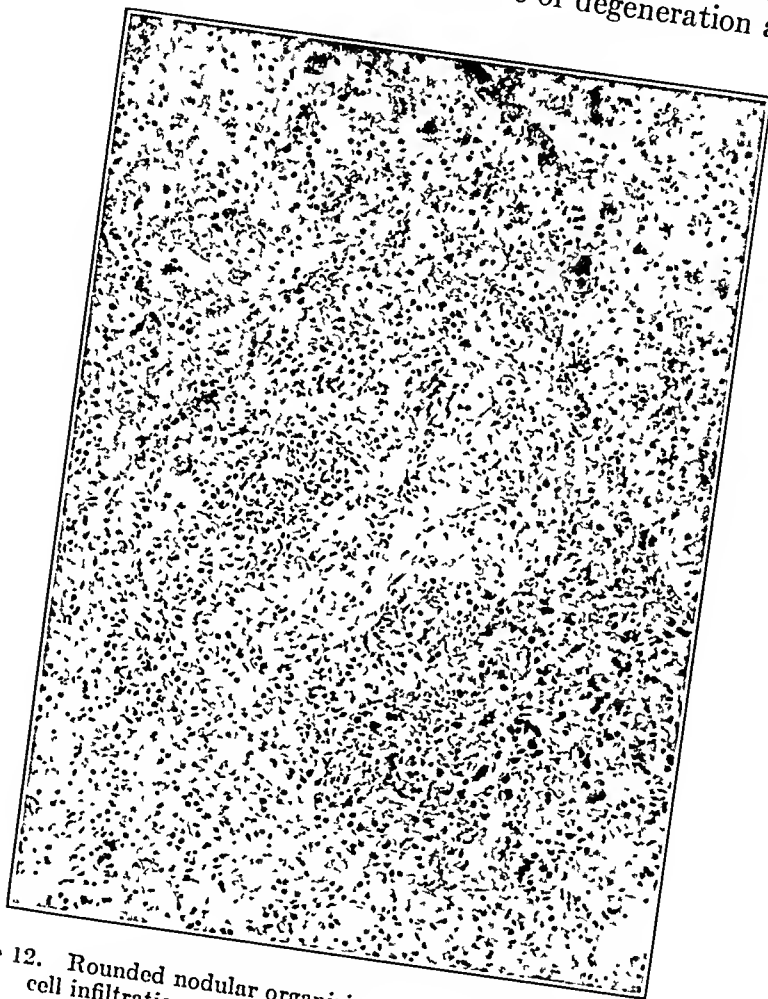


FIG. 8.—Case 12. Rounded nodular organizing zone. Note vascularization, round cell infiltration and fine fibrillar collagen. ($\times 175$)

tion. Usually the cells in the reticularis are more deeply stained, often showing brownish pigmentation due to lipochrome, with a more intense and compact eosinophilic staining of the cytoplasm. pyknosis of the nucleus, and general shrinkage and atrophy. In some of the focal zones showing progressive cytonecrosis, identical retrogressive changes were noted. At the periphery of centrally placed areas of coagulation necrosis, similar involutional changes were often seen in cortical cells. One gains the impression that the cyto-

necrotic areas described may actually represent exaggerated involutional phenomena normally noted in the reticularis. In like manner the foci of frank coagulative necrosis suggest an acute sudden response on the part of the cortical cells of an exaggerated nature and somewhat functional significance. It should be emphasized at this point that only cases which illustrated foci of actual necrosis of coagulative type or of progressive cytonecrosis of cells were included in this series. Foci of degeneration and atrophy seen within reticularis or other layers of the cortex, without necrosis, were excluded from consideration.

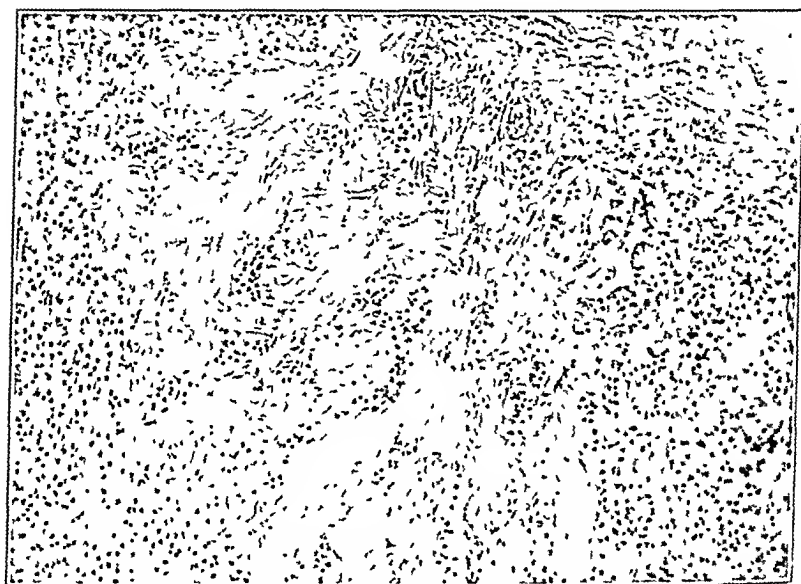


FIG 9 —Case 3. Larger area of fibrous scarring extending from capsule in upper portion of field through glomerulosa and fasciculata. Note coarse fibrillar collagen ($\times 175$)

The phenomenon of focal necrosis in a solid parenchymal organ such as the liver has often been observed. Some have been established to be bacterial in origin, as in typhoid. Necrotic foci of identical nature have been seen in a compact endocrine organ like the pituitary gland. Such foci of necrosis, both in the pituitary and the adrenal vary in size. Complete necrosis of the pituitary giving rise to dramatic endocrine syndromes occurs especially associated with pregnancy. It is conceivable that areas of focal necrosis of the adrenal cortex may increase in size, merge and otherwise involve an extensive area sufficient to cause clinical symptoms of adrenal insufficiency. The presence of parallel degenerative and necrotic changes in a case of Addison's disease studied in this laboratory, associated with widespread fibrosis of the cortex acquires significance

on this basis. The atrophy and fibrosis repeated the changes noted above in the zones of focal necrosis undergoing organization. In several of the focal areas studied, intense congestion of the sinusoids and hemorrhage was found limited to the areas of necrosis and the immediate vicinity. In one instance fibrinoid material was found in the center of a lesion. Such findings represent a replica in miniature of the adrenal changes seen in the Waterhouse-Friedrichsen syndrome.



FIG. 10.—Case 11. Sharply delimited zone of hyalinized fibrotic and ossified area with beginning central marrow formation. ($\times 175$.)

The findings of these small areas of focal necrosis of the adrenal cortex has no clinical application at present. It may be significant, however, in providing illustrative material for the basic mechanism operative in those widespread necrotic lesions giving rise to dramatic syndromes. In Case 18, a condition of profound shock following trauma was associated with focal necrosis of the adrenal and active acute ulcerations of the duodenum. This parallels the findings of McLaughlin for such a correlation. There also exists the possible

significance of the summation of recurring focal lesions in producing a progressive insufficiency or predisposing to a subsequent severe acute episode. Quite theoretical is the consideration of allergic sensitization to such specific cortical tissue with subsequent hyperergic reaction.

The gradation in size of the foci of physiologic and degenerative changes and the small areas of focal necrosis, to the widespread diffuse lesions with established clinical syndromes suggests that attention might well be focussed on establishing a relationship or common denominator between the two.

Giemsa stains and Gram preparations on most of the acute necrotic lesions failed to demonstrate virus inclusions on bacteria *in situ*.

Summary. 1. Eighteen cases of focal necrosis of the adrenal cortex are presented.

2. The literature is reviewed and the etiologic factors of infection, toxemia, endocrine factors, and allergy, discussed.

3. A physiologic component in the production of the necrotic lesions is indicated by the multiplicity of etiologic factors, the apparent significance of endocrine states, and the gradation of such lesions in size and nature with involutional physiologic changes in the adrenal, and the negative bacteriologic and virus findings.

4. The possible significance and the relationship of such lesions to Addison's disease and to Waterhouse-Friedrichsen syndrome and to intestinal ulceration is intimated.

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A PLATELET-RED CELL CONJUGATION PHENOMENON AND ITS RELATION TO BLOOD COAGULATION

By SAMUEL PENNELL, M.D.

ASSISTANT HEMATOLOGIST, ASSISTANT TRANSFUSIONIST, BROOKLYN JEWISH HOSPITAL
BROOKLYN, N. Y.

(From the Departments of Hematology and Laboratories, Brooklyn Jewish Hospital)

THE blood platelets have been studied very extensively but in most of the studies reported in the literature it has generally been considered that they carry out their mission in the coagulation process as individual agents. Very few observers have linked the function of the platelets to other formed elements in the blood.

The purpose of this paper is to call attention to a conjugation

phenomenon between the blood platelets and the red cells in normal blood, and to discuss the significance of this relationship in the light of the more recent knowledge of blood coagulation.

Hayem,⁸ in 1889, studying fresh preparations of shed blood, noted that the red blood cells frequently fragment when included in a mass of degenerating platelets. Tait,¹⁴ in 1918, in studies on clotting frogs' blood, described a property of the blood cells which manifests itself by red cells and platelets adhering to one another. He calls this "selective adhesion," and states: "When a film of frogs' blood clots, a coarse network of fibrin-like material is formed. Each node in this network consists of either a mass or a single thrombocyte around which the erythrocytes arrange themselves in rosettes. Not all the erythrocytes are involved, but only those lying in the vicinity of the thrombocytes. That portion of the involved erythrocyte which lies in immediate contact with the thrombocyte becomes constricted as if with a purse string . . . the skin of the erythrocyte apparently adheres to the thrombocyte." This phenomenon is not an accidental occurrence but a deliberate "selective adhesion" only between the red cells and platelets, for he goes on to state: "On the other hand I have seen a granular leukocyte crawl from a distance to such a mass of thrombocytes and pursue its course over and past them, being in no wise impeded by contact with them."

This phenomenon may readily be observed in normal freshly shed human blood, both in dried stained smears and in moist preparations. When such specimens are examined under the oil-immersion lens, one can observe that where the platelets lie in contact with red cells, the red cells usually have become deformed. The extent of the red cell deformities run the gamut from that of slight indentation to complete division or actual fragmentation. Careful focusing further reveals that the contours of these deformities conform closely to the shape of the adjacent platelets, and that the edges of the deformed areas are rough and ragged, in contrast to the smooth unaffected edge of the rest of the red cell (Fig. 1).

Conforming to Tait's¹⁴ observations in frogs' blood, not all of the human red cells are involved and the phenomenon is strictly a selective one, taking place only between the red cells and platelets (Fig. 2).

If a small drop of freshly shed normal human blood is placed on a slide, allowed to remain undisturbed for about 1 minute and then spread by dropping a coverslip over it, the red cell platelet conjugation can readily be observed. In such a preparation, clumps and masses of platelets can be seen which have one or more deformed red cells enmeshed among them.

In these wet preparations one can readily note the absolute selectivity of the phenomenon, for the leukocytes can be seen either at rest among the red cells or floating past them, but never becoming involved in the process.

The Effect of Anticoagulants. *Sodium Citrate.* When smears are made from both citrated and unmodified samples of the same blood, the citrated smears show a striking difference in the red cell platelet conjugation when compared to the unmodified smears. The smears of citrated blood show practically no deformed red cells, and the platelets for the most part lie freely in the spaces between the red cells. Only after diligent search can one find an occasional deformed red cell with its attached adjacent platelet (Fig. 3).



FIG. 1

Study of moist preparations of freshly citrated blood fails to show the presence of the agglomerations of platelets around enmeshed and deformed red cells, which are so readily seen in similar preparations of unmodified blood. The platelets are neither clumped nor attached to the red cells; few if any deformed red cells are seen; and the platelets individually and in small groups, lie about freely in the plasma between the red cells. It is interesting to note in this connection that Ferguson,⁴ studying platelets under dark field illumination, found that in citrated plasma the platelets lose their "stickiness," but that when the plasma is recalcified, the platelets regain this stickiness and agglutinate in the usual manner.

Heparin, In Vitro. Fresh heparinized blood examined either in a dried stained smear or moist coverslip preparation also shows a marked diminution of the red cell platelet conjugation. In the moist preparations the platelets are not clumped around red cells, and in the dry smears practically no deformed red cells in conjunction with platelets can be seen.

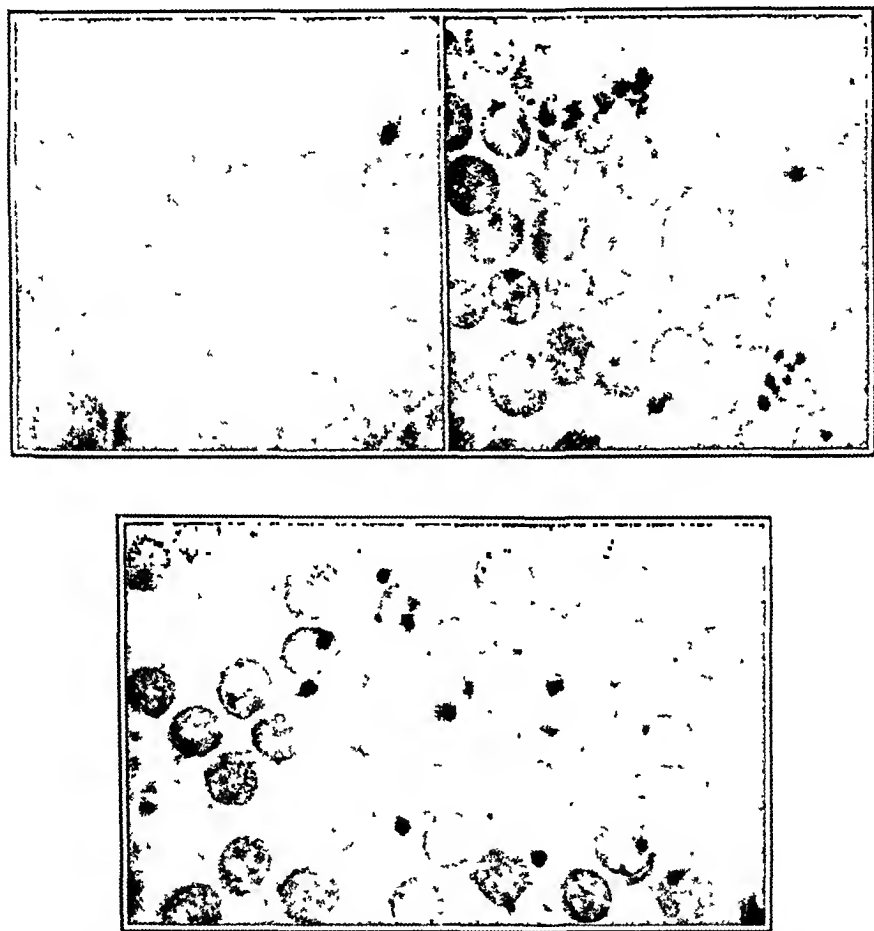


FIG. 2

Heparin, In Vivo. Stained smears and moist preparations of normal unmodified rabbit's blood show the red cell platelet conjugation to a greater degree than normal human blood. If, however, sufficient heparin solution is given intravenously to a rabbit to produce a prolongation of his coagulation time from the normal of about 4 minutes to over 24 hours, blood smears made during this period of prolonged coagulation show a marked diminution of the red cell-platelet conjugation. Although occasional deformed red cells with their adjacent platelets may still be found, they are scarce and the platelets generally are seen to lie freely in the areas between the red cells.

When the effect of the heparin has worn off and the rabbit's coagulation time has once again returned to normal, the red cell-platelet conjugation can again be observed to the normal degree in the blood smears and wet preparations.

Bleeding States. Blood from cases of thrombocytopenic purpura and hemophilia were studied because of the contrasting hematological defects in these two diseases. In thrombocytopenic purpura, while the platelets are greatly reduced in number, the coagulation time of the blood is fairly normal, while in hemophilia, although the platelets are normal in number, the coagulation time is usually prolonged. It was thought, therefore, that if the red cell platelet conjugation played some rôle in blood coagulation, it might become evident in a comparison of these two contrasting conditions.

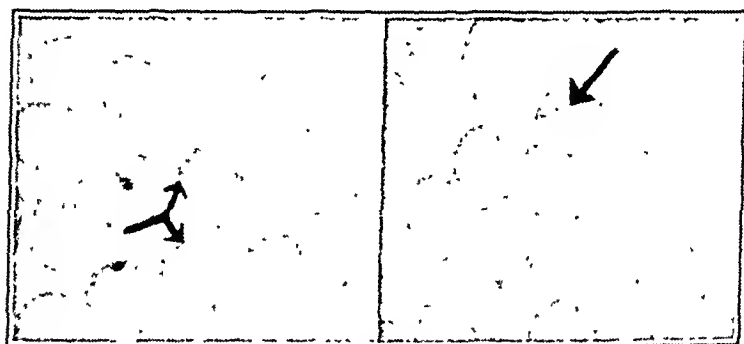


FIG. 3

Thrombocytopenic Purpura. Blood smears made from freshly shed unmodified blood in cases of thrombocytopenic purpura, often require prolonged and diligent search to find the few platelets which are present. However when they are found, they are almost without exception, seen to be in contact with one or more red cells, and these show the deformities previously described (Fig. 4).

In normal blood not more than perhaps 25% of the platelets seen in the smears are found in conjunction with deformed red cells, while in thrombocytopenic purpura, where a scarcity of platelets exists, 80% to 90% are found to bear this relationship to the red cells. In this disease, although the platelets are decreased in number, the red cell platelet conjugation is relatively increased rather than diminished to parallel the numerical reduction of the platelets.

Hemophilia. In cases of hemophilia, during periods when the coagulation time is markedly prolonged, and there have been no recent transfusions, blood smears as well as moist preparations consistently show marked diminution of the red cell platelet conjugation as compared to normal blood.

In the dried smears, the conjugation is not entirely absent, but

is encountered very infrequently as compared to normal blood. Here and there, in the hemophiliac blood smears one may find an occasional deformed red cell in contact with a platelet, but these are few in number. This diminution, although difficult to determine numerically, is nevertheless very apparent and the manner in which most of the platelets lie about in the spaces between the red cells is quite unlike their appearance in normal blood (Fig. 5).

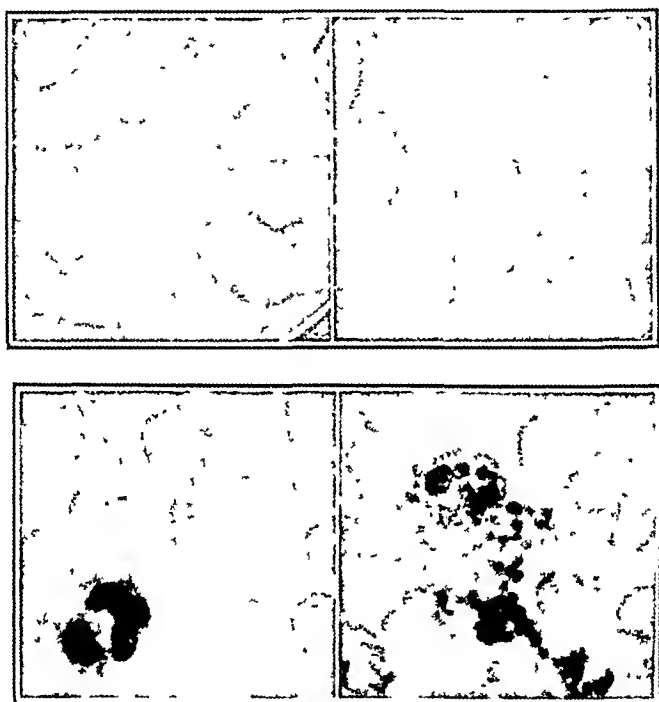


FIG. 4

Moist preparations of hemophiliac blood also show practically no red cell platelet conjugation. The platelets do not agglomerate around the red cells as they do in normal blood, but lie about singly or in small groups between the red cells in an innocuous manner. These moist preparations of hemophiliac blood resemble very closely those of citrated and heparinized blood described previously.

Discussion. Practically all the theories of normal blood coagulation, Morawitz,¹² Howell,⁹ etc., accept the breakdown of the platelets and the consequent release of a ferment (thromboplastin—thrombokinase) as the earliest step in the coagulation process. The circumstances which induce the platelets to degenerate have been the subject of much and varied discussion in the literature. The most commonly accepted idea is the one suggested by Morawitz,¹² that when blood is shed the platelets come in contact with a water wettable surface and disintegrate, thrombokinase (thromboplastin) being freed in the process. The liberated thrombokinase

then acts as the trigger mechanism which sets off the complex series of chemical interactions, the end-result of which is clot formation.

Howell¹⁰ states: "It would seem that in the circulating blood the content of thromboplastin must lie below the concentration required to induce prompt clotting. When blood is shed or withdrawn the content of thromboplastin is increased with some suddenness, by the mass disintegration of the platelets, to a concentration sufficient to cause clotting within a few minutes."

If, in order to degenerate rapidly and *en masse*, the platelets need to make contact with some surface, it appears that the blood, by employing the red cell platelet conjugation herein described, has at hand a constantly available mechanism of its own which fulfills such a requirement, without assuming the need for extraneous aid, such as Mornawitz's¹² water wettable surface.



FIG. 5

It would seem that the platelets use the surfaces of the red cell for the physical contacts which they require in order to undergo rapid degeneration. The inability of blood to clot in the blood-vessels under normal conditions can be attributed to the motion of the blood preventing sufficient contact to permit conjugation.

Donahue and Howell² have shown that there is a destruction of platelets as the blood passes through the capillary areas of the systemic circulation. Since platelets and red cells come into intimate contact in the capillaries, it is possible that the destruction of platelets as noted by these authors results from the red cell platelet conjugation which occurs in the capillaries. The process is no doubt lessened by the fact that the blood flow in the capillaries, although sluggish, never becomes completely stagnant. The destruction of some platelets in the circulation is apparently the source of the minimal amounts of thromboplastin which are always found to be present.

When blood is shed and becomes completely stagnant, the platelet red cell conjugation, now unhampered by the blood flow, proceeds to such an extent that rapid mass degeneration of the platelets occurs. Under these conditions the quantity of thromboplastin

produced rises quickly to a concentration sufficiently high to set off the clotting process.¹⁰

Anticoagulants and Blood Dyscrasias. We may assume from their staining characteristics that the red cells, taking the acid stain, carry a negative charge, and the platelets, taking the alkaline stain, carry a positive charge. It is a fundamental law of physics that particles which carry opposite electric charges, when suspended in a liquid, are attracted to one another and when they collide their charges tend to become neutralized. If, as it is believed, the integrity and well-being of living cells depend on the maintenance of the electric charges which they normally carry, contact between the red cells and platelets with the consequent neutralization or loss of the platelet's normal charge may cause it to disintegrate very rapidly. In fact, changes in the electric charges of the platelets in clotting blood have actually been measured by Steuber and Lang.¹¹

It seems logical to assume, therefore, that the anticoagulants, sodium citrate and heparin, which interfere with the red cell-platelet conjugation, do so because they disturb the electrolytic relationship which these formed elements normally maintain in relation to one another. Sodium citrate is, of course, an electrolyte, while evidence that heparin acts electrolytically is presented by Ferguson and Glazko,⁵ who show that it functions like a polyvalent anion.

Studies on hemophiliac platelets by Howell,¹⁰ Birch,¹ Quick¹³ and Govaerts and Gratia⁷ have demonstrated that while they remain in his own blood, the hemophiliac's platelets are "resistant" and do not disintegrate readily. However, when removed from hemophiliac blood, they lose this resistance to disintegration and behave exactly like platelets from normal blood. Further, Howell¹⁰ has demonstrated that the only difference between normal and hemophiliac plasma is that the hemophiliac plasma contains less thromboplastin. This lowered level of thromboplastin is no doubt the direct result of the greater stability of the hemophiliac's platelets.

Since the defect in hemophilia appears to be the resistance to disintegration of the hemophiliac's platelets and since this resistance disappears when the platelets are removed from the hemophiliac's blood, one may assume that some factor present in normal blood which permits platelets to disintegrate is absent in hemophiliac blood. Because of the absence of this factor, the hemophiliac platelets, although they have the potentiality to disintegrate,^{1,7,10,13} cannot do so.

In view of the ample amount of red cell-platelet conjugation in normally clotting blood and its striking diminution in hemophiliac blood, together with the fact that the hemophiliac platelets disintegrate normally when removed from the hemophiliac blood, one is confronted with the possibility that the red blood cells are an important and perhaps indispensable factor in the process which causes the breakdown of the platelets. The hemophiliac's red cells may

thus differ from the normal in that they lack some factor, the absence of which does not allow the red cell platelet conjugation to occur. In consequence the hemophiliac's platelets cannot disintegrate and thus appear to be resistant.

On this basis, it would only be necessary to make available normal red cells for the hemophiliac's platelets in order for them to undergo normal disintegration. Thus a transfusion of normal blood to a hemophiliac, supplying many normal red cells, may enable his platelets to disintegrate and reduce the coagulation time as well as help check the bleeding.

Two facts concerning the formed elements in circulating blood pointed out by Foster⁶ in 1880, and Eberth and Schimmelbusch⁷ in 1888, offer an explanation for the lack of intravascular clotting which might result from the red cell-platelet conjugation and its consequent platelet degeneration.

Foster⁶ showed that "When fine particles of several kinds, some lighter than others, are driven through a narrow tube, the heavier particles flow in the axis and the lighter in the more peripheral portions of the stream." Later in 1888 Eberth and Schimmelbusch⁷ showed that the formed elements of the blood, as they are propelled in the blood stream, arrange themselves similarly. The red cells form a central core, the leukocytes a concentric cylinder about the red cells and the platelets move along at the periphery of the stream nearest the vessel wall.

The dynamics of the circulation thus keeps the red cells and platelets apart until they reach the capillaries. Here they are forced into contact with one another, for the channels are so small that the cells pass through almost in single file. The electrolytic attraction of red cell and platelets also aids the mechanical forces in bringing about the red cell platelet conjugation in the capillaries.

The small amounts of thromboplastin formed from the disintegration of the platelets as a result of the red cell platelet conjugation in the capillaries, however, is not sufficient to produce intravascular clotting.

When normal blood is shed and lies completely stagnant, the behavior of the red cells and platelets is no longer controlled by the flow. The platelets and red cells, attracted now only by their opposite electric charges, gravitate unrestrainedly toward one another. The platelets being smaller, mass in clumps about the red cells, their electric charges become neutralized and they disintegrate *en masse*, liberating large amounts of thromboplastin. The amount of thromboplastin thus liberated is sufficient, in spite of the antiprothrombin present, to cause coagulation.

As previously demonstrated, the red cell-platelet conjugation is markedly diminished in the hemophiliac's blood, perhaps because of some defect in his red cells. Few platelets can thus degenerate

his circulation and the lowered content of thromboplastin in his blood⁶ may thus find explanation.

One cannot overlook the interesting possibility that the red cells which are involved in the conjugation are also destroyed along with the platelets. Hayem,⁸ actually saw these red cells fragment when included in a mass of degenerating platelets.

Conclusions. 1. From the knowledge now available, in order for shed blood to clot, a sudden and massive disintegration of platelets appears to be necessary.

2. A conjugation phenomenon between platelets and red cells is described which is regarded as providing a means by which the platelets can employ the surfaces of the red cells for the contacts necessary to carry out this mass disintegration.

3. The reduction in platelets which normally occurs as the blood passes through the systemic capillaries may be due to a limited amount of red cell-platelet conjugation which takes place during the transit of the blood through the capillaries.

4. It is demonstrated that the anticoagulants, sodium citrate and heparin, interfere with the red cell-platelet conjugation.

5. The phenomenon is shown to be markedly reduced in hemophilia and relatively increased in thrombocytopenic purpura.

6. The fact that the hemophiliac's platelets have been shown to be normal in various ways would seem to indicate that the hemophiliac's red cells may be responsible for the diminished red cell-platelet conjugation in this disease.

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TUBERCULOSIS IN INDUSTRY*

By H. R. EDWARDS, M.D., F.A.C.P.

DIRECTOR, BUREAU OF TUBERCULOSIS, DEPARTMENT OF HEALTH
NEW YORK, N. Y.

TUBERCULOSIS has been a problem in industry for many years and from all available evidence is most likely to increase at the

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present time. Industry is now operating at its maximum and is, therefore, placing a greater strain on the worker than ever before. This increased strain will, without doubt, cause many breakdowns of those infected as well as many who are accepted into industry with latent or unhealed lesions. This increased hazard will result in lowering of productive output for the individual with the lesion and at the same time it will expose countless other workers to infection, and many will later succumb to the disease and thereby become progressively less productive.

There are thousands of workers entering industry today that would not have the same opportunity in more normal times. The high wages offered and the chance for independence will attract many workers, some of whom know they have tuberculosis but who are willing to take the chance with the hope that they will make the grade. There will be thousands of young women entering the factory and experience indicates that some will develop the disease as a matter of course. Their infection may occur inside or outside the plant but the continuous physical strain will lower their resistance permitting a tuberculous infection to develop into actual disease.

Workers today are moving from place to place in the country where jobs are available. Thus, those from low rate areas will go to areas with high tuberculosis rates and *vice versa*. In many instances housing will be inadequate causing congestion and, therefore, greater opportunities for the spread of infection not alone to the worker but to members of his family as well.

We are now entering an era of rationing of foodstuffs with a promise that more is to come, and as the war conditions continue we may expect to see a definitely lowered standard of living which is invariably associated with increases in tuberculosis. In the past, the existence of a state of war has always resulted in an increase in tuberculosis, and without doubt the situation today, which involves civilians almost as much as the armed forces, will bring greater strains on the civilian population than ever before. The successful outcome of this global conflict will depend as much on the output of industry as the tactical forces in the field. Therefore, those of us who must remain in civilian life must exert every possible effort to prevent further spread of infection in the community and this is a problem not alone of industry and its immediate workers but their families as well.

The spread of tuberculosis is conditioned in large part by the number of infectious cases in the community. The exposure of the worker to silica dust is the one agent of industry recognized to effect the susceptibility of the worker to tuberculosis. Other industrial agents have little, if any, effect on the individual insofar as tuberculosis is concerned. The problem of silicosis today is much less significant than formerly and, in addition, it is a problem

that can be very largely controlled through proper engineering procedures. Silica dust is limited to a few industries and, therefore, only a small percentage of all workers will ever be exposed to this extra risk. Thus, as important as silicosis may be as a clinical entity, or as a factor which increases susceptibility to tuberculosis, it constitutes but a small part of the problem of tuberculosis in industry.

Tuberculosis control programs have been developed by some of the larger industrial establishments in this country with great success. Many large industries have not developed such programs, and as a rule the thousands of small industries are without any program for the health of their employees. Selby⁹ of the General Motors Corporation has stated that the purpose of industry is manufacturing and that to justify a medical service it must hold down the time lost by illness or injury. To quote him further, "So the over-all problem of tuberculosis control in industry is one of general community concern. It cannot be segregated within industry. . . .

"So far as industry itself is concerned the sound long-range program is to clear the plant of tuberculosis and to keep it clear. This does not necessarily imply that all workmen who have tuberculosis are unemployable. It does mean that they must be employed only under conditions that permit them to work in safety to themselves and their fellow-employees and they must have close medical supervision."

The responsibility that may be assumed by industry in this matter is well illustrated by the program at the Michelin works in France.¹⁰ The management of this company became interested in the tuberculosis problem early in this century. In 1915 they made allowances to families with a tuberculosis problem. By 1932 these allowances were made compulsory by law for all industries in France. In 1920 slum dwellings were torn down and replaced with model houses at modest rentals, and by 1932 all slum areas had been removed. In 1921 a dispensary was established for the tuberculous and pretuberculous by the Michelin Company. In 1922, 13% of new cases of tuberculosis were reported as in the advanced stages of the disease but by 1935 this percentage had fallen to 1.5%. Between 1931 and 1936 new cases reported fell from 181 or 8.2 to 84 or 3.8 per 1000 of the population.

There are a number of large industrial establishments in this country which grant special privileges to their employees who fall ill with tuberculosis, but none who also assume the complete family problem.

In New York City since 1933 the Department of Health has conducted an aggressive case-finding program among the apparently healthy adult population in selected groups.² In 1939, the first surveys were conducted in labor groups. The aim of these surveys

in industrial groups was to demonstrate the problem that existed and find a reasonable method for the conduct of routine surveys. It was hoped, once the problem was known and a method for its solution presented, that the worker and management might be brought together and establish a routine service. We have demonstrated in a number of surveys the prevalence of disease,^{1,3,4} but we have not been able to induce labor to set up a continuing program of its own nor to induce labor to join with management in a program for tuberculosis control. This failure is, undoubtedly, the result of the distrust labor has of the attitude management might take in discharging men on the basis of the findings. It is, of course, possible to exaggerate many of the lesions that might be found in routine chest radiography, but it is believed, as indicated by Selby,⁹ that in a joint program, adequate safeguards could be set-up that would protect the worker. If a laborer is suffering from an active or infectious tuberculosis, it is to his own advantage to seek proper care, and it is to the advantage of his companions to be protected from possible infection. The advantages to industry are obvious to all.

The surveys in labor groups in New York City have, therefore, been arranged entirely with labor organizations and never with management. Where cases have been found in need of care a way has always been found to induce the worker to accept treatment. Following some of our surveys the unions have contributed in excess of \$10,000 in sick benefits and the payment for hospital care for their members.

The success of our program in various groups has been determined primarily by the interest and enthusiasm of the leaders of the union involved. Where this interest is dynamic the coöperation has reached as high as 70% of the union membership, and, conversely, where the union leaders were more concerned with routine union problems and treated the survey as a desirable but extra duty, the coöperation has been as low as 12%.

Between January, 1941, and up to July of 1942 a total of 15,644 individual members of 13 unions and 8 defense plants have been x-rayed and are reported here for the first time.

Of the above total, 10,168 were x-rayed in 1940 and 1941, and 5,476 have been x-rayed in 1942 and are directly related to defense industries and two large commercial airlines. Some comment is necessary on the two groups as they were approached in a somewhat different manner. In the first group the unions involved for the most part approached the Department requesting a survey. Every effort was made to point out to the leaders of the various unions the estimated prevalence of disease expected, the importance of the survey, etc. Usually conferences were arranged with shop foremen to explain the program, the successful methods of approach in other surveys, and to answer any questions they might have. Then the

union by letter, posters and by word of mouth from the leaders and shop foremen endeavored to sell the idea to the rank and file of the membership. By and large in these surveys the percentage of co-operation was low compared to that in certain of the textile surveys previously reported, and it is believed that it was due primarily to the inability of the union leadership to put the program over, and to the fear of the worker that he might lose his job. In one of these unions (cooks and elcfs) a strong appeal was made to them on the basis that if their membership could say that all were x-rayed and found free of tuberculosis there would result a decided economic gain to the membership, for they would then be offering a preferred worker to the trade.

In the defense workers surveys started in the early summer of 1942; the approach was made to them as a joint enterprise by the Department of Health using its WPA project, and the Queens Tuberculosis and Health Association. The latter organization served as a promotion agency by providing lectures, literature, posters and motion pictures, and in addition a worker to assist in making arrangements with union leaders and management. It is believed that such a combination of forces comprised an ideal method for utilizing the official and voluntary agencies resources to the best advantage. The Department of Health provided the technical services as in all other surveys.

At the outset, an attempt was made to secure the joint coöperation of labor and management in this program, because it was felt that such programs should become a routine for pre-employment as well as the regular periodic examination of employees. The first approach was made to labor leaders. As a result of preliminary discussions it became obvious that labor did not want to enter a joint program with management. Labor did not want management to be in the position of saying that they had given labor the service even though the entire program would be provided without cost to either. This was unfortunate because it later proved difficult in several instances to arrange for a set-up of the Roentgen ray unit in the shop where the service would have been more convenient to the worker and would, undoubtedly, have resulted in a much higher attendance. Even though union headquarters were located not far distant from the plant, there was evident a reluctance on the part of the men to come for Roentgen ray before or at the close of a shift.

This program is being continued and it is hoped that a joint effort by labor and management can ultimately be achieved.

Results of Surveys. The results of the first group of surveys are shown in Table 1. As these studies are made up of a number of different types of workers, some of which are small in number, they are being presented in less detail as compared to previous reports on surveys.² Instead of 5 year age divisions the mean age has been computed. By color, the material was predominantly white as

88.28% were so classified, 7.26% were negro, 4.16% Puerto Rican, and 0.3% unspecified. Approximately 80% of the individuals were males. Of the white, 80.75% were males. Of the negro, 65.72% were males; of the Puerto Rican, 74.7% were males, and of the others unspecified, 96.77% were males.

TABLE 1.—THE PREVALENCE OF TUBERCULOSIS BY ROENTGEN RAY EXAMINATION OF 10,168 UNION WORKERS IN NEW YORK CITY, 1910-1911

Type of population	Number x-rayed			Mean age	Number and per cent with tuberculosis					
					Active pul. tbc.*		Arrested		Primary	
	Total	M	F		No.	%	No.	%	No.	%
Food Trades	1,128	1,120	8	39.8	11	0.98	42	3.72	173	15.31
National Maritime Union . .	1,812	1,790	22	36.5	20	1.10	62	3.42	335	17.94
United Furniture Workers . .	421	395	26	30.9	4	0.95	7	1.66	63	14.96
Bleachers and Dyers	470	463	7	34.2	7	1.49	8	1.70	50	10.64
United Electrical Workers . .	1,108	1,051	57	33.1	4	0.36	22	1.99	101	9.12
Chain Restaurant Workers . .	1,127	883	244	42.2	5	0.44	48	4.26	218	19.31
Amalgamated Meat Workers . .	194	194	..	34.6	1	0.52	2	1.03	40	20.62
Laundry Workers	391	197	194	38.9	1	0.26	18	4.60	61	16.37
Dept. Store Joint Board . . .	113	61	52	32.2	.	.	8	7.08	16	14.16
United Office and Proff. Workers	1,110	488	622	29.4	.	.	22	1.98	130	11.71
American Communications Assn.	564	330	234	30.5	2	0.61	16	2.81	72	12.77
Hat Block and Dyers	202	202	.	37.7	.	.	15	7.43	25	12.38
I. L. G. W. U. Needle Trades .	1,528	906	622	29.0	14	0.92	38	2.49	126	8.25
Totals	10,168	8,080	2,088	34.5	69	0.68	308	3.03	1,403	13.90

* Active and clinically significant.

There were 69 cases of significant tuberculosis found in this entire group, 86.96% of which were in the white, 5.8% in the negro, 7.25% in the Puerto Rican and none in the unspecified groups. The white males accounted for 82.61% of all significant lesions in the entire group. Likewise, the 305 arrested pulmonary lesions were more prevalent in the white than other races. The percentage being 91.15%, in the negro 3.28%, in the Puerto Rican 5.57% and in the unspecified group 0.98%.

The 10,168 workers included in Table 1 represented 13 different union groups of widely varying types of occupation. There were 2449 members working in various food trades ranging from 0.19% to 0.98% of clinically significant tuberculosis.

There were 1812 members of the National Maritime Union with a prevalence of significant tuberculosis of 1.1%. The membership of this union is considerably larger than the numbers here reported, and from previous knowledge of the apparent frequency of tuberculosis among laborers of this class, it is believed that an even higher rate would be found among a more random sample.

The highest prevalence rate of significant pulmonary tuberculosis in this group, 1.49%, was found among members of the Bleacher and Dyers Union. On the other hand, it is interesting to note that they showed a much lower than average prevalence rate for chronic pulmonary tuberculosis (significant and arrested) and primary type lesions than for this group as a whole. There is no evidence to

suggest that this higher rate bears any direct relation to an occupational hazard in the industry. As the number of individuals reported here represents a substantial number of the entire membership, the results may, therefore, be considered as a fair sample of all workers.

It is of interest to note that no significant cases were found in the Department Store Joint Board members, though so small a number x-rayed is not a basis for any conclusion. The United Office and Professional Workers, predominantly females, revealed no active lesions. The Hat Bleachers and Dye Workers were small in number and showed no cases of significant tuberculosis. In each of the three foregoing groups a number of arrested cases were found.

The results of the examination of defense workers are shown in Table 2. The population in these surveys was made up almost exclusively of the white race. Thus, analysis by color is of no significance.

TABLE 2.—THE PREVALENCE OF TUBERCULOSIS BY ROENTGEN RAY EXAMINATION OF 5476 WORKERS IN INDUSTRIES DEVOTED TO DEFENSE ACTIVITIES IN NEW YORK CITY, 1942

Organization	Number x-rayed			Mean age	Number and per cent with tuberculosis lesions					
					Active*		Arrested		Primary	
	Total	M	F		No.	%	No.	%	No.	%
Fairechild Aviation Corp.	577	477	100	29.39	5	0.87	17	2.94	49	8.49
Premier Metal Company	290	199	91	31.40	1	0.34	8	2.76	29	10.0
Kollsman Instrument Company	1,484	1,051	433	29.80	8	0.54	40	2.7	137	9.23
American Seal Cap Corp.	188	87	101	28.51	3	1.6	4	2.13	16	8.51
Morey Machine Company	419	400	19	37.03	2	0.48	20	4.77	63	15.03
General Bronze Company	663	651	12	34.07	3	0.45	34	5.13	72	8.6
Pan American Airlines	615	475	140	25.19	2	0.33	5	0.81	44	7.15
American Airlines	1,240	999	241	26.35	3	0.24	21	1.69	132	10.65
Totals	5,476	4,339	1,137	29.57	27	0.49	149	2.72	542	9.9

* Active and clinically significant.

The division by sex in this group of workers is quite similar to that of the union workers in Table 1. This is, undoubtedly, caused by the preponderance of males in the Airlines, General Bronze Company and the Morey Machine Company. Of the two groups, the United Office and Professional Workers and the American Seal Cap employees were the only groups that had a preponderance of female workers.

There were 27 (0.49%) of the defense workers group that were classified as having significant pulmonary tuberculosis. The prevalence of arrested and primary lesions were also less than in the union workers in Table 1. The generally lower prevalence of disease may be in part a reflection of the lower average age of defense workers as compared to union workers. Also it may be presumed that the 1855 employees from airlines were selected for their work with greater care than in other industries. The prevalence rates in the

airline employees were 0.33% and 0.24%, which are the lowest rates for any of the groups in the two studies, excepting the Laundry Workers with 0.26%. It is not believed that a more representative sample of Laundry Workers would show so low a rate.

It was expected that silicosis might be found with some frequency in some of these industries. In the General Bronze Company there were 7 cases or slightly better than 1%. There were 2 cases in the employees of the Kollsman Instrument Company.

It is obvious, therefore, from this sample of defense workers that excessively high tuberculosis rates are not apparent. In fact, they are lower than for union employees regularly employed in commercial industries. Also they are lower than the prevalence rates found among draftees in New York City which have averaged about 1%. It should not be assumed from this study that the tuberculosis problem in defense industries as shown by this sample is of minor importance as the numbers involved are too small for such a conclusion.

Discussion. The findings in these studies are fairly typical of similar examinations by others and again confirm our previous observations that as a group the employed population invariably reveals less significant pulmonary tuberculosis than those unemployed and on relief. It is also obvious that the prevalence of tuberculosis varies considerably on the basis of occupation, but that so far as evidence is available there is no reason to believe that the occupations studied here can be considered as direct causative agents in tuberculosis.

It is of interest to point out the rather high prevalence of chronic pulmonary tuberculosis of an arrested type noted in the workers in these groups. These lesions, based on all acceptable criteria, are of long standing and for the most part give no evidence of potential danger in the future unless some untoward circumstances arise that will materially lower resistance. Further evidence of this fact has been found in our surveys which have frequently included repeated survey examinations of the same individual and that have shown no change in their lesions. This point has been emphasized in the studies of Sawyer⁵ and Reid⁷ in which they have followed such cases over varying periods of time.

The foregoing studies, as well as our own, indicate the need for sound clinical judgment in the evaluation of such lesions in pre-employment examinations as well as those found in surveys of industrial workers. It is well to remember that the lesion found at a given examination represents the accumulation of pathology over the years up to that time. The proper evaluation of such lesions will prevent the unnecessary hospitalization of many of these individuals or the exclusion of the individual from work. This policy has been followed in the handling of pre-employment as well as other types of studies by this Department with the result

that many individuals with lesions apparently arrested have been continued in their positions while periodic Roentgen rays confirm their stability. Also in our experience, it is found that approximately one-half of the lesions originally classified as significant on the survey radiograph will later be found to be arrested. In many of these lesions the individual is allowed to continue his regular activity during the period of supervision. The period and frequency of supervision varies according to the individual ease and character of the lesion. These lesions are of decidedly more importance in the younger age groups, the females and colored.

Thus, if properly handled, these surveys of industrial workers need not jeopardize the job of the worker. On the other hand, if he does have an active tuberculosis, he should not expect to be allowed to continue in his job where he will be a potential source of danger to his fellow workers.

Reid⁷ and Fellows^{5,6} have reported extensively on the program at the Metropolitan Life Insurance Company. Their studies indicate that following the pre-employment examination and the annual reexamination, new lesions will develop. The average incidence rate for the 10 year period, 1930 to 1939 inclusive, was 2.12 per 1000 males per year and 2.58 per 1000 females per year, the rate for females being the greatest between 20 and 24 years, and the rate for males exceeding the female peak but occurring at ages above 40 years. The periodic annual reexamination has resulted in a steady decline in prevalence from 0.4 in 1930 to 0.1 in 1939. Fellows points out that there was no significant difference in the development rate of pulmonary tuberculosis in employees whose first roentgenogram was classified as negative when compared to a similar group whose first roentgenogram showed a healed primary. Both authors point out the increased prevalence of pulmonary tuberculosis among pre-employment groups as compared to regular employees. Undoubtedly, the routine supervision of employees detects lesion in their early stages and thereby prevents the development of advanced infectious cases.

Reid⁷ reported on 139 pre-employment cases of apparently arrested chronic pulmonary tuberculosis at time of first roentgenogram and reevaluated in 10 years. There was no conclusive evidence of reactivation during that time, though 1 case was so reported elsewhere but not confirmed, and another had an unstable lesion by Roentgen ray but no signs of symptoms or institutional supervision. Sawyer⁸ indicates that in 75 arrested or inactive cases, that 16% of the minimals relapsed in from 1 to 5 or more years, whereas, 52% of the advanced cases relapsed. These cases were drawn from employees that cured for tuberculosis and later returned to work and, therefore, are not comparable with the cases found in pre-employment examination by Reid. As a result of the program conducted by Sawyer, there has been a reduction in the

cation for the establishment of a tuberculosis control program in all industries. Such a program is greater than can be handled by the local Department of Health and is a responsibility that should be shared jointly by management and organized labor.

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ASPIRATED BONE MARROW STUDIES IN NORMAL MACACUS RHESUS MONKEYS.*

BY R. M. SUAREZ, M.D., F.A.C.P.,

R. S. DIAZ-RIVERA, M.D.,

AND

F. HERNANDEZ-MORALES, M.D.,

SAN JUAN, PUERTO RICO.

(From the Department of Internal Medicine, University Hospital, School of Tropical Medicine.)

THIS paper is published chiefly for investigators working with monkeys. The literature on the hematologic findings in monkeys, contains but few publications on peripheral blood, and none at all on the bone marrow picture of this animal.

The peripheral blood picture of the monkey has been discussed in some 24 publications, the most recent being published in 1938. Scarborough,⁹ in an analysis of the published data, calls attention to the deficient study of many of the blood constituents.

According to Scarborough⁹ the red blood cells in the monkey are biconcave discs, showing some variation in size. Rarity of abnormal forms is the rule, and polychromatophilia is moderately frequent. Hayem³ failed to encounter nucleated cells in the peripheral blood of the monkey after studying 4 different species. Anderson and Neill¹ found but one nucleated cell in 10 monkeys studied. Krumbhaar⁶ determined that the average of reticulocytes in monkey blood (*Macacus*) is around 0.3%, with a normal range of from 0 to

* This work was performed on *Macacus rhesus* monkeys living in Santiago Island Colony approaching the most natural of habitats for these animals. The island is located about 1 mile from the eastern coast of Puerto Rico, and the primate colony is maintained under the auspices of Columbia University.

0.8%, the reticulations being more delicate than in man or other animals. The size of the erythrocytes is equal to those of man, the average diameter being 7.1 micra (Hayem³).

The average number of total red blood cells reported by four authors,^{1,3,7,13} and recapitulated by Scarborough,⁹ is around 5,590,000 per emm. with a normal range of 5,000,000 to 7,000,000. Krumbhaar and Musser⁷ did not find influence of age or size of the animal upon the number of red blood cells.

Results from studies in 36 animals demonstrate that the hemoglobin estimation varies tremendously as put forth by three different authors.^{1,5,7} Minima of 63, 73, 88 and 85% are reported; averages of 75, 67, 85, 103 and 95%, maximums from 82 to 115%. As these estimations were performed under widely different conditions and methods, a great variation is to be expected.

Krumbhaar and Musser⁷ described the polymorphonuclear neutrophils as having as many as 10 to 15 lobules in their nuclei, and the lymphocytes, as being larger than in man. Lucas and Prizer⁸ found that it was difficult to differentiate the large lymphocytes from the monocytes. The total number of leukocytes as reported by nine investigators^{1,3,4,7,8,11,12,13} average 16,210 per emm. (range 8000 to 25,000), the average differential findings being:

	%.	Range.
Polymorphonuclears	42.2	30-50
Lymphocytes	52.8	40-60
Large mononuclears or transitionals	1.5	1-12
Eosinophils	3.7	1-5
Basophils	.32	.1- .5

The average count of platelets in the peripheral blood stream of the monkey, as reported by Krumbhaar and Musser,⁷ is 267,000 per emm., with a variation from 155,000 to 424,000.

As explained before, no comparison can be established in our bone marrow studies, since we have been unable to find citations in the literature in relation to this subject. In Table 3 we have added a comparison with normal human marrow (sectioned), as given by Custer and Krumbhaar.² They obviously have used different criteria for allocating nucleated red cells, polys and lymphocytes than those used in this study.

Materials and Methods. Bone Marrow Studies. Forty healthy Macacus rhesus monkeys were submitted to bone marrow aspirations; 21 were male and 19 females, with ages ranging from 6 months to 12 years, and weight oscillating between 1.5 and 11.5 kilos. There were 4 infants, 8 young and 28 adults.

The marrow was aspirated through an 18-gauge needle attached to a 20 cc. syringe, since strong negative pressure is needed to obtain even minute quantities of marrow. The animal was tied to a table, the head turned to one side, and the mid-sternum was cleaned up with iodine and alcohol. The needle was introduced in the midline, and the site of greater resistance was located in the sternum. Then the needle was screwed obliquely at an angle of 45° into the marrow cavity with very slight pressure.

TABLE 1.—BONE MARROW PICTURE OF MACACUS RHEBUS MONKEYS, COMPARED WITH THE ADULT HUMAN.

	Infant monkeys (4).		Young monkeys (8).		Adult monkeys (28).		Normal human.	
	Range, %.	Average, %.	Range, %.	Average, %.	Range, %.	Average, %.	Range, %.	Average, %.
<i>Sternal Marrow.</i>								
Megakaryoblasts	0-1.0	0.37	0-1.0	0.24	0-0.8	0.15
Early erythroblasts	0 2-3	1.32	0-1.6	0.91	0-4.5	0.99
Late erythroblasts	2.0-9.3	5.82	0.4-7.5	4.73	0-10.0	4.35
Normoblasts	6 7-20.5	12.3	7.0-14.2	10.79	3.0-20.4	10.30	...	14.8
Total (red cell series)	10.5-31.0	19.82	10.6-21.0	16.69	18.2
Myeloblasts	0-0	0	0-0.5	0.11	0-0.5	0.11
Promyelocytes	0.5-0.7	0.5	0-1.0	0.6	0-0.5	0.11
Eos. myelocytes	1.5-13.5	5.42	0-1.0	0.62	1.2-13.0	1.18
Meta-myelocytes	0.5-1.0	0.67	3.4-9.5	5.8	0-1.5	1.25
Poly. neutrophils	0-0.5	0.12	0-2.4	0	0-0.4	0.33
Poly. eosinophils	4.5-6.0	5.2	0-0	5.49	2.5-18.0	0.03
Poly. basophils	34.5-45.0	40.05	1.5-15.0	2.15	25.0-60.5	7.18
Total (granulocytic series)	1.0 4.0	2.3	37.6-49.5	0.17	0-7.5	46.86
Lymphocytes	0 0.3	0.2	0-4.0	0	0-1.2	1.86
Monocytes	43 0-07.5	0.2	0-0.5	57.5	...	0.08	...	3.0
Plasma cells	12.0-33.3	25.57	8.6-34.0	25.2	40.0-78.2	61.89
Megakaryocytes	0-0	0	0-0.2	0.05	5.8-47.2	21.57	...	63.8
Total	0-0	0.07	0 0	0.56	0-0.6	0.11
	12 0 33 6	25.65	9 2-34 8	25.81	0-2.5	0.62
					0 0.2	0.01
					7 8 47.4	22.31	...	3.2

Aspiration at times was quite difficult, yielding marrow for only a few smears, due to the scarcity of the material and to its richness in fat. The sternum of the monkey is quite soft, and cartilaginous or soft bone is often traversed by the needle with no obtention of marrow. Thus, it is advisable to perforate the hardest portions of the bone that are usually encountered in the midsternum.

Smears of the marrow were made and studied after having been stained with the Jenner-Giemsa stain. Differential counts were performed in all the 40 bone marrow specimens; an average of 500 cells being counted in each.

Results. Infant Monkeys. In 4 infant *Macacus rhesus* monkeys, the bone marrow differential counts yielded the following results (see Table 1): The megaloblasts appeared to be scarce. The early erythroblasts ranged between 0 to 2.5% (average, 1.32%), while the late erythroblasts had a variation between 2 and 9.3% (average, 5.82%). The normoblasts were present in percentages between 6.1 and 20.5 (average, 12.3).

There were no myeloblasts in any of the samples of the infants' bone marrow and but few premyelocytes. There was an average of 5.2% metamyelocytes and 40.05% of adult neutrophils. Eosinophils and basophils were scarce.

The lymphocytes ranged between 12 and 33.3% in four samples, while plasma cells were rare.

Young Monkeys. The marrow of 8 young monkeys was studied (see Table 1). Megaloblasts showed about the same percentage as in the infants. Both early and late erythroblasts were slightly fewer than in the infant monkeys, while the normoblasts were fewer.

Myeloblasts were found in only two samples. The premyelocytes doubled the count in infants; the neutrophilic, eosinophilic and basophilic myelocytes were about the same. Metamyelocytes and adult polymorphonuclears averaged much the same as for the infants.

There were as many lymphocytes in the bone marrow of the infant as in the young animals; but we found some monocyte and plasma cells in the marrow of the young monkeys.

Adult Monkeys. We studied 28 adult *Macacus rhesus* monkeys in the same way as with infants and young (see Table 1). In this series all the elements of the red cell series were slightly less common than in the other two series.

Myeloblasts were still rare, but the premyelocytes doubled the averages of the infants and young. The metamyelocytes ranged higher than in infant and young monkeys. Adult polymorphonuclear neutrophils amounted to a little more than in the younger animals, while polymorphonuclear eosinophils and basophils averaged a little less than in the young and infant monkeys.

The lymphocytes appeared almost equal to the count in infants, but fewer than in young animals. The monocytes were found to

be present in larger numbers in the adults than in the younger animals. The percentage of plasma cells was a little higher than in young, and very much greater than in the infant animals. In none of the samples were megakaryocytes encountered, except in two adults.

The erythrocytic component of the bone marrow in infant and young monkeys is found to be higher than in the adult animals. The granulocytic component is higher in the adult than in either young or infant, and there is a gradual decrease with age, in contrary to the erythrocytic component. The lymphocytic series were in total higher in the infant and young than in the adult animal. It is interesting to notice that even in the adult monkeys, the lymphocyte count was high.* Ratios of erythrocytic to granulocytic series were as follows: Infants, 1 to 2.8; young, 1 to 3; and adults, 1 to 4.

Morphologically, the cells resemble those of the human bone marrow. The number of lobes of the nuclei of the polymorphonuclears were numerous in some cases. The lymphocytes appeared to be larger in size than in human marrow and a great number showed many coarse granules in the cytoplasm. With the exception of 2 cases, megakaryocytes were totally absent. Many "loose" nuclei resembling reticulo-endothelial cells were encountered, but in a very few cases was a definite cytoplasmic component seen in these cells.

Comment. In this study it should be noted that these monkeys live in the most natural of habitats and were caged only for a day or two before our experiments were practiced. Thus, the animals led their natural life as nearly as possible.

The bone marrow picture of the infant monkey was characterized by a higher count in megaloblasts, early erythroblasts, late erythroblasts and normoblasts than in the young or adult animals; but the number of cells of the granulocytic series was lower in the infant than in the young or adult. The lymphocytes were more numerous in the infants' marrow than in the adults', but equal to the young animals. The same thing may be said about the bone marrow of the young monkey, which appeared to present the same picture as the infant in relation to the adult.

The ratio of the erythrocytic series to the granulocytic series gradually decreased with age. Megakaryocytes were found only in two adult samples. Tables of ranges and averages in per cent for each of the cellular components of the bone marrow are presented in this paper.

* The difficulty of distinguishing between lymphocytes and the more immature types of nucleated erythrocytes in the bone marrow suggests another possible explanation for this observation.—EDITOR.

Summary. 1. Forty *Macacus rhesus* monkeys were submitted to bone marrow aspirations in order to study the marrow picture of this animal.

2. All the monkeys, of which 4 were infants, 8 young and 28 adults, live in the most natural of habitats, approaching the most perfect way of life for the animal.

3. The average erythrocytic series in the infant is higher than in either young or adult marrow.

4. The average granulocytic series is higher in the adult than in either infant or young; the young animals' marrow being richer in those cells than the infants'.

5. The young monkey has more erythrocytic cells in its marrow than the adult.

6. The lymphocytes are more numerous in the infant and the young than in the adult monkey's marrow.

7. The ratio for erythrocytic and granulocytic components were found to be as follows: For the infant 1 to 2.8, for the young 1 to 3, and for the adult 1 to 4.

8. Morphologically the cells of the bone marrow resemble those of the human, except for the multiple lobulations of the nuclei of the polymorphonuclear leukocytes and for the larger size of the lymphocytes of the animal.

9. Megakaryocytes were seen in very low percentages (0.2) in only 2 adult animals; none were seen in either young or infants.

10. If it were not for the high number of lymphocytes the bone marrow of the monkey would approach the picture of the human at different stages of life.

This work could not have been possible without the cooperation of Mr. Michael Tomlin in charge of the Cayo Santiago Primate Colony, and the valuable and disinterested technical assistance of Misses Rosario Viquez and Clemencia Benitez to whom we are greatly indebted.

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STUDIES ON THE HEMORRHAGIC AGENT
3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN)

PART III. A REPORT ON FURTHER CLINICAL OBSERVATIONS*

By JAMES B. BINGHAM, M.D.

INSTRUCTOR OF MEDICINE

OVID O. MEYER, M.D.

ASSOCIATE PROFESSOR OF MEDICINE

AND

BERYL HOWARD, B.S.

TECHNICAL ASSISTANT

MADISON, WIS.

(From the Department of Medicine, University of Wisconsin Medical School)

In previous publications^{2,11,12} we reported on 3,3'-methylenebis (4-hydroxycoumarin),† a drug that has become available synthetically through the work of Link and his associates.^{4,5,6,8,13,17} It is the purpose of this report to briefly cite other experiences which indicate additional possible usefulness of this drug.

Previous papers have demonstrated that Dicumarol is capable of prolonging the prothrombin time and coagulation time in dogs and human beings *in vivo* when administered orally, or intravenously in the form of disodium salt. The effects are noticeable only after 24 hours or more, regardless of the size of the dose. The drug is reasonably safe, but because individual responses vary considerably, the dosage must be controlled by daily or almost daily determinations of the prothrombin time and coagulation time. In most instances these roughly parallel each other. The drug appears to have no effect on the functions of the liver or kidneys as tested by the prothrombin time, the hippuric acid test of Quick,¹⁶ the cephalin-cholesterol flocculation test of Hanger,⁷ determination of the serum proteins and non-protein nitrogen, urinalysis, and the phenol-sulphonphthalein test before and after the periods of observation. In 29 dogs, several of which were killed with the drug, no significant hepatic or renal changes, either gross or microscopic, were demonstrated. On the other hand, rather widespread dilatation of capillaries, arterioles and venules was frequently noted. In human beings no toxic manifestations other than hemorrhage were demonstrated; this was ordinarily microscopic, but in 1 instance, gross hemorrhage from the operative site. Vitamin K, even when administered in large doses, did not reduce the prolonged prothrombin time, but transfusion of fresh blood was antidotal.

It was concluded that the drug might well have a place in clinical

* This investigation has been aided in part by a grant from the Wisconsin Alumni Research Foundation.

† Dicumarol is the collective trademark for 3,3'-methylenebis (4-hydroxycoumarin) of the Wisconsin Alumni Research Foundation which controls the use thereof.

medicine in the prevention of thromboses and as a substitute for heparin in other conditions. It should, however, be used with caution; patients with hemorrhagic tendencies or gross hepatic disease should not receive the Dicumarol. The proper dosage, in our experience, varies with the patient, but 80% of our cases responded satisfactorily to an original dose of 5 mg./kg. followed by the daily administration of 1.5 mg./kg. On certain days no dose was given if the prothrombin time or coagulation time was too prolonged. The aim was to maintain the prothrombin time at about 15 seconds, not beyond 19 seconds (25%), and the coagulation time between 15 and 20 minutes. Since the early reports appeared, others^{1,10,18,19,20} have made clinical studies, and in the main these corroborate the experiences of Butt, Allen and Bollman² and our own.

Methods. The methods employed have been described in previous papers. For each patient a complete blood study and routine urinalysis was made. No patient was given the drug before the bleeding time, coagulation time, prothrombin time, and capillary fragility were measured. The normal prothrombin time, measured by the method of Quick as modified by Pohle and Stewart¹⁴ was 9.5 to 10.5 seconds. Always the technique and potency of the thromboplastin were checked by testing one or more untreated individuals each day. The coagulation time was measured by the 2-tube method of Lee and White,⁹ as modified by Pohle and Taylor.¹ The normal time by this method is, in our hands, between 6 and 14 minutes.

Use With Heparin. It is obvious that the latent period of 24 hours or more is disadvantageous to the patient with a recent thrombosis. Hence the possible value of using an anticoagulant during the latent period was considered. It has already been stated that there was no theoretical objection to the use of heparin and Dicumarol combined. The case described below, 1 of 3 treated with both heparin and Dicumarol seems to demonstrate the value of the simultaneous use of the two substances.

CASE 1.—A 62-year-old white male, a railroad engineer, was admitted (service of Dr. M. G. Masten) on 12-9-41. On the previous day he had developed numbness and weakness of the left arm and leg. These symptoms increased. For a month he had had some pain in the occipital region. Physical examination showed alertness, weakness of the left hand and left side of the face, some dysarthria, deviation of the tongue to the left, tortuosity of the retinal arteries, and a blood pressure of 170/104. It was believed that the patient had a cerebral thrombosis; later it was concluded that the occlusion was of one of the ascending branches of the middle cerebral artery. On the day of admission the coagulation time and prothrombin time were both normal, and heparin was administered subcutaneously and Dicumarol orally. The total dosage of heparin during the 3-day period of its administration was 395 mg. The response to these drugs is shown in the chart. The recovery was rapid and the patient left the hospital on 1-10-42. Follow-up studies in the outpatient department have shown a satisfactory condition, and the patient has been back at work.

The chart shows that the prothrombin time increased on the third day of Dicumarol administration. With this evidence of the effectiveness of the drug, the heparin was stopped, and Dicumarol alone was administered. It appears that this procedure is logical and worthy of consideration in cases

where immediate prolongation of coagulation is desirable, although there is no question that intravenous is preferable to subcutaneous administration of heparin.

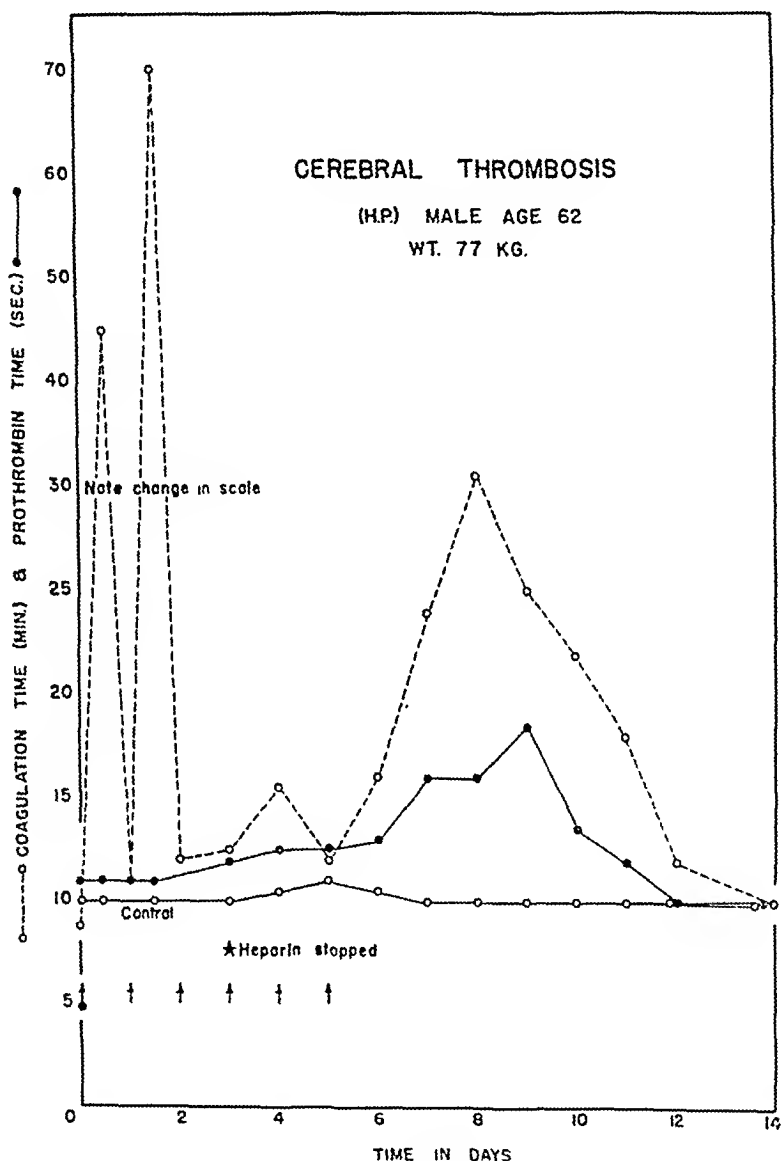


CHART 1.—The effect of combined administration of heparin (total of 395 mg.) and Dicumarol (♂ = initial dose of 5 mg./kg.; † = daily dose of 1.5 mg. kg.) upon the coagulation time in a case with cerebral thrombosis.

Subacute Bacterial Endocarditis. The results of the combined use of heparin and sulfonamides in the treatment of subacute bacterial endocarditis have not, in many instances, been happy. Fatal cerebral hemorrhages have been reported. On theoretical grounds the employment of Dicumarol in combination with a sulfonamide is less logical than the use of heparin. Nevertheless, because of several inquiries we treated 2 cases, 1 a boy of 14 with pneumococcus

Type VI infection engrafted upon a rheumatic endocarditis, and a second case, shown in Chart 2. The first patient was treated for only 15 days, the second for a total of 81 days (50 days of which are

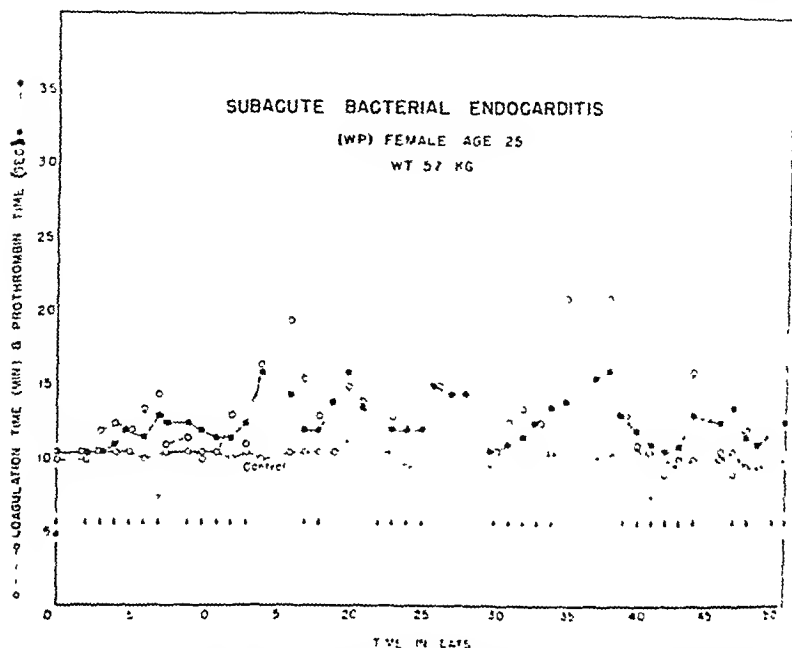


CHART 2.—The effect of the administration of Dicumarol combined with sulfadiazine for a protracted period to a patient with subacute bacterial endocarditis (streptococcus viridans; \bullet = 5 mg./kg., \circ = 1.5 mg./kg.; T = transfusion of blood).

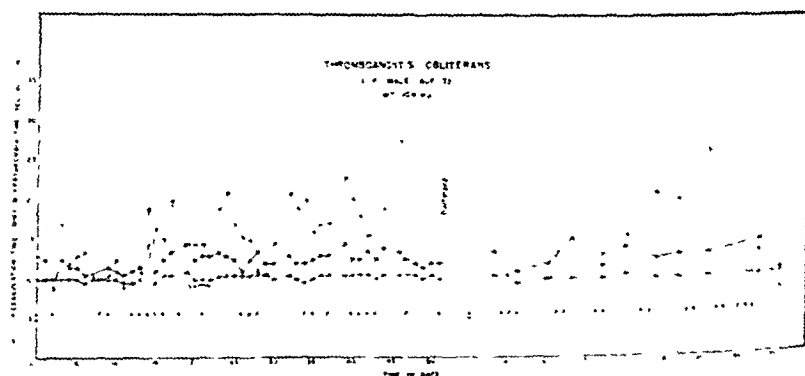


CHART 3.—The effect of prolonged administration of Dicumarol to a patient with Buerger's disease. Total dosage approximately 10 gm. (\bullet = 5 mg./kg.; \circ = 1.5 mg./kg.; ∇ = 3 mg./kg.).

depicted in the chart). In neither instance was any untoward effect observed, nor was any benefit demonstrated, although the coagulability of the blood was decreased in both. In the patient treated

for 81 days the liver function was unaffected by the protracted administration of Dicumarol. This patient died of her disease on June 12, 1942, more than 5 weeks after the Dicumarol was stopped. Gross and microscopic postmortem studies of the liver and kidneys showed only the changes attributable to subacute bacterial endocarditis. Despite these 2 cases, however, in which no accident occurred, the use of Dicumarol is deemed unwise, as others¹ have observed cerebral hemorrhage and death resulting from this type of therapy. Allen¹ has advised that the drug be avoided or used only with great caution in subacute bacterial endocarditis.

Prolonged Use of Dicumarol. In occasional cases it may be desirable to administer Dicumarol for periods of many weeks. In the light of the case reported above and that depicted in Chart 3, this is regarded as permissible.

CASE 2. A white male of 32, with mild thromboangiitis obliterans, obtained relief of pain during treatment, but whether or not the Dicumarol was responsible was not definitely established. Thus far he is the only patient that has been treated as an out-patient, and then only after a considerable period of hospital observation, and the only patient that was not observed almost daily with determinations of the prothrombin time and coagulation time. Liver function tests at the conclusion of the period of treatment were normal, as they had been prior to the institution of therapy. During the 92-day period of treatment the drug was administered 62 times for a total of approximately 10 gm.

Case With Hemorrhage. Although the appearance of blood in the urine as demonstrated by a positive benzidine test is not unusual, and may occur in about 15% to 20% of cases treated with Dicumarol, gross bleeding occurred in only 2 of the first 100 cases treated. The first experience of bleeding from an operative site has been reported. A second case is here reported, because this patient was more sensitive to Dicumarol than any other we have encountered.

CASE 3. A white male of 65 was admitted to the Urological Service on 3-5-42, with the complaint of bloody urine. Cystoscopic inspection of the bladder demonstrated a carcinoma, and on 3-23-42 a total cystectomy and prostatic enucleation were performed. Because of the wide exposure of the pelvic veins, administration of Dicumarol was advised. On 3-24-42 the patient received a total of 325 mg. (5 mg./kg.) and on 3-25-42, 98 mg. (1.5 mg./kg.). The drug was then stopped because of the unusually prompt and marked effect. Gross hemorrhage was observed 2 days later, as depicted in Chart 4. Undetected hemorrhage may have been present elsewhere, for the hemoglobin fell from a preoperative level of 11.8 gm. to 6.4 gm. on 3-30-42. A persistent anemia was noted thereafter and only gradually did the hemoglobin increase to 10.1 gm. by 5-2-42. His condition was precarious. It was deemed necessary to give 5 transfusions, each of 500 cc., between 3-28-42 and 4-1-42, 2 of them on 3-28-42. The patient finally improved sufficiently to be discharged on 6-6-42.

This patient had had cyclopropane-ether anesthesia. The question immediately comes to mind, Did the anesthesia impair the liver so that the patient was thus more markedly affected by the Di-

cumarol? The assumption is logical if we accept the theory that the action of Dicumarol depends upon physiologic inhibition of the liver. Also, a Hanger's test in this patient was ++ on 3-28-42, but negative on 4-7-42. This matter has been recently investigated by testing the relative sensitivity of anesthetized and unaesthetized dogs.

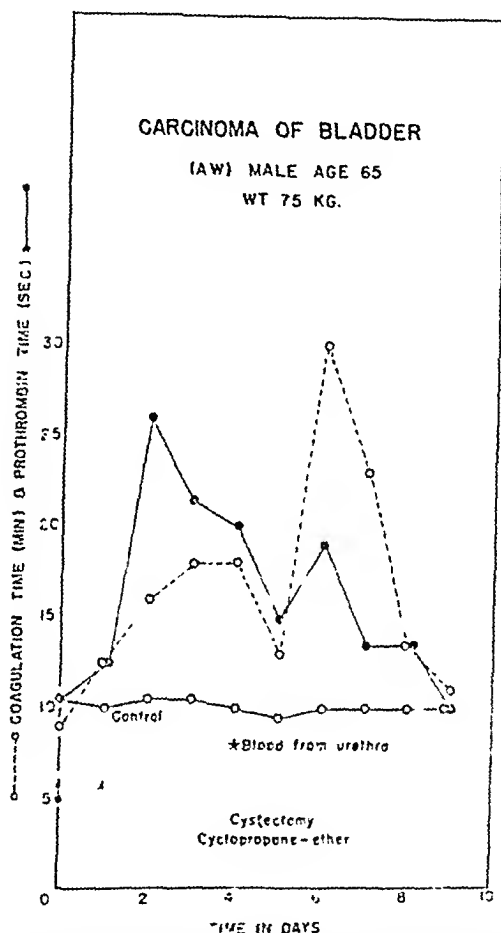


CHART 4.—The marked effect of administration of Dicumarol to a postoperative case. Cyclopropane-ether anesthesia was administered for about equal periods for a total of 80 minutes ($\frac{1}{2}$ = 5 mg. kg.; $\frac{1}{4}$ = 1.5 mg. kg.).

Effect of Dicumarol on Anesthetized Dogs. Three dogs were anesthetized with cyclopropane for 30 minutes and 3 additional dogs were anesthetized for 45 minutes with cyclopropane and ether for equal periods. The last 3 dogs were given $\frac{1}{4}$ gr. (0.015 gm.) to $\frac{1}{3}$ gr. (0.020 gm.) of morphine subcutaneously 2 hours prior to the induction of anesthesia; the first 3 received none. On the day after the anesthesia, each dog was given 5 mg. kg. of Dicumarol orally, and the 3 unaesthetized control dogs were given a similar dose.

The total doses ranged from 47.5 to 116 mg. Thereafter for 10 days the prothrombin time and coagulation time were measured daily. The response in the unanesthetized dogs was as marked as in the experimental animals; hence no increased sensitivity of normal animals was discernible. This lessens the likelihood that anesthesia was responsible for the condition in the above-described patient, but it does not, of course, exclude the possibility, nor does it obviate the necessity of attention to this detail in other postoperative cases.

Discussion. It is hoped that the report of these additional experiences with the use of Dicumarol will be of aid to others who are employing or plan to employ this interesting drug in clinical investigations. As our experience has grown, we have used it with less and less fear of untoward effects. It is still our feeling after treating 105 patients that an approximate oral dose of 5 mg./kg. followed by the daily administration of 1.5 mg./kg. is reasonably satisfactory and gives the most stable level of prolonged prothrombin time and coagulation time, although repeated doses at intervals of about 3 or 4 days are also permissible. When the disodium salt of 3,3'-methylenebis (4-hydroxycoumarin) is given intravenously, it is our custom to give 4 mg./kg. at intervals of 3 to 5 days. No matter how the drug is administered, repeated (preferably daily) determinations of the prothrombin time and coagulation time is imperative. The induction of a prolongation of the prothrombin time to below 25% of normal is almost certainly unwise, and probably maintenance of the coagulation time at between 15 and 20 minutes is satisfactory.

Dicumarol is still in the stage of active investigation, and its indiscriminate use is hazardous. It has, however, been demonstrated that it may be given for periods as long as 90 days without producing subjective symptoms or detectable undesirable objective findings. The mechanism by which the drug acts has not yet been established, and one should be on guard for the possible ease with an idiosyncrasy whence, on theoretical grounds at least, one might anticipate the production of serious hepatic disease. To date, we have not experienced any untoward effect other than hemorrhage from operative sites.

The question of the actual value of Dicumarol in preventing thrombosis in patients, a question of major importance, is still unsettled, and only extensive investigations with large, well-controlled series will furnish the answer. The theoretical basis for its use is sound, for when properly used it is capable of producing hypocoagulability of blood.

Conclusions. 1. Continued studies with Dicumarol-3,3'-methylenebis (4-hydroxycoumarin) have further established its efficacy in prolonging the prothrombin time and coagulation time in human beings.

2. Administration of Dicumarol may be safely combined with heparin administration when prompt prolongation in the coagula-

tion time is desired. When the prothrombin time is prolonged, evidence of Dicumarol effectiveness, the heparin may be omitted.

3. The use of sulfonamides and Dicumarol in combination does not appear to be of value in the treatment of subacute bacterial endocarditis. This therapy is not advised.

4. As much as 10 gm. of Dicumarol has been administered over a 92-day period to a patient with thromboangiitis obliterans with symptomatic improvement, and without detectable changes in liver function.

5. A second case with gross hemorrhage from an operative site after a small total intake of Dicumarol is reported. It was suggested that general anesthesia such as cyclopropane ether, which was used in this case, might possibly make the patient more sensitive to Dicumarol. Possibly smaller than average doses should be employed. However, experimental studies in dogs do not substantiate this tenet.

6. The initial dose of 5 mg./kg. followed by daily doses of 1.5 mg/kg. still appears to us to be reasonably satisfactory in most patients.

7. Reiteration of the importance of caution in employment of this potent drug is deemed proper. Dicumarol is still under investigation, and should not be used unless thoroughly reliable facilities for daily accurate determinations of the prothrombin time and coagulation time are readily available.

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BOOK REVIEWS AND NOTICES

OUTLINE OF PSYCHIATRIC CASE-STUDY: A Practical Handbook. By PAUL WILLIAM PREU, M.D., Assistant Professor of Psychiatry and Mental Hygiene in the Yale University School of Medicine, Physician-in-Charge of the Psychiatric Clinic of the New Haven Hospital, Associated Psychiatrist to the New Haven Hospital. Pp. 279. Second Edition. New York: Paul B. Hoeber, Inc., 1943. Price, \$2.75.

STIMULATED by the methods of Adolph Meyers and others, the author brought together the material for his first edition 3 years ago. The Outline is intended as an aid in bringing out the facts upon which the diagnosis and treatment shall rest.

The first part of the book is an Outline of Psychiatric History-Taking and Behavioral Examination for Use With the Adult. It includes the complaint, present social situation, background of the problem, family history, social-psychiatric history, personality, medical history and previous psychiatric illness or problem. Included in the Behavioral Examination are general appearance, behavior attitude content, topics of preoccupation, emotional state, stream of speech, consciousness, memory, intellectual capacity and insight. A special part considers procedure when the patient is stuporous or comatose.

The second section discusses the Outline of Psychiatric History-Taking and Behavioral Examination for Use With the Child, where much of the information is obtained from the mother or other interested person. Such data is often more complete than that given by an adult whose early life cannot be recalled. The subject matter of this handbook is well suited to the purpose designated. N. Y.

VIRUS DISEASES. By Members of the Rockefeller Institute for Medical Research; THOMAS M. RIVERS, M.D., WENDELL M. STANLEY, PH.D., LOUIS O. KUNKEL, PH.D., RICHARD E. SHOPE, M.D., FRANK L. HORSFALL, JR., M.D., and PEYTON ROUS, M.D. Pp. 170; several plates. Ithaca, N. Y.: Cornell Univ. Press, 1943. Price, \$2.00.

THIS book consists of the Messenger lectures, given at Cornell University by 6 specialists in the field of viruses. Thomas M. Rivers discusses the nature of viruses. He takes as an example vaccinia and tells what has been learned of its physical, chemical and immunologic properties. Under the electron microscope, the elementary bodies appear to have some sort of internal structure and a limiting membrane.

W. M. Stanley speaks of passing viruses through suitable hosts, thus causing the viruses to mutate. It is such mutants that are used in immunizing against smallpox, rabies and yellow fever.

Swine influenza is discussed by R. E. Shope. Between epizootes, the virus lurks in an intermediary host, the lung worm, which itself has an intermediary host, the earth worm.

Human influenza is divided by F. L. Horsfall into pandemic, epidemic and endemic types. For each type he discusses the etiologic rôle of viruses and bacteria.

Which tumors are caused by viruses and how these agents act to cause tumors, is the subject of the lecture by Peyton Rous.

These lectures are quite readable, are not highly technical, and bring the subject up to date. M. M

PSYCHOSOMATIC MEDICINE: The Clinical Application of Psychopathology to General Medical Problems. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University Medical School, and O. SPURGEON ENGLISH, M.D., Professor of Psychiatry, Temple University Medical School. Pp. 687. Philadelphia: W. B. Saunders Company, 1943. Price, \$8.00.

ONE of the latest developments in our profession is the appearance of psychosomatic medicine, about which a special periodical is already published. This subject, "at the present time embraces the neuroses plus an extension of our knowledge of the neuroses to the psychopathology of other conditions previously thought to be in the realm of purely physical medicine." It is claimed one-third of all patients come under this classification, and that another third show symptoms dependent in part upon emotional factors. "The busy practitioner can read the first two chapters and the last four and get a general idea of the subject." As here described, the psychologic relation of the mental processes, shows a decided Freudian coloring; in the diagnosis of personality trends, high tribute is paid to the somewhat neglected Rorschach ink-blot tests.

Throughout the 23 chapters there are 73 case reports. The part on the gastro-intestinal system in 3 chapters includes functional digestive disturbances, chronic appendicitis, gall bladder disease, mucous colitis, ulcerative colitis, cardiospasm, anorexia nervosa, and peptic ulcer. Genito-urinary and sexual disorders consider instinctual forces, genital functioning, education in sexuality, emotions and menstruation, dysmenorrhea, amenorrhea, frigidity and impotence. Three chapters on the endocrine system and metabolism, include emotional life and ovarian function, menopausal syndrome, male climacteric, puberty, relation of disorders of the thyroid gland, Addison's disease and the adrenal syndrome, diabetes mellitus, hyperinsulinism, and obesity.

A chapter on military medicine is well balanced. In a few chapters some subjects are considered too briefly, such as alcohol and drug addicts, which are accorded scarcely a dozen lines. There is a want of formal neurologic examinations. Being teachers, these authors advocate first-year instruction in psychobiology to parallel that of physiology and anatomy. In the second year the psychologic processes of adolescence should be correlated with those of physiology and endocrinology. The third year should give combined lecture and case presentation. In the final year, that knowledge already acquired should be applied in the ward, class and clinic. The book gives many references and a comprehensive index covers more than 26 pages.

N. Y.

UNDERSTAND YOUR ULCER. By BURRILL B. CROHN, M.D., Associate in Medicine, Gastro-Enterology, Mt. Sinai Hospital, New York; Associate in Medicine, Columbia University. Pp. 199; 19 illustrations. New York: Sheridan House, 1943. Price, \$2.50.

IN this book Dr. Crohn has done for the peptic ulcer patient what Dr. Joslin has done for the diabetic. It is the sort of book every gastro-enterologist has wanted to write. It covers the things the ulcer subject should know and what any good personal physician would tell him if he had the time. Many will not agree with every statement, but for the lay reader's sake the author has done well to avoid controversial issues and has shown excellent judgment, without misleading his reader, in omitting observations that might produce undue alarm. Part II, on diets, by SYLVIA BAYARD, is well done and will be found extremely helpful not only to the ulcer patient but also to the practising physician. Dr. Crohn is to be congratulated on a work that is certain to be popular at this time and to require many revisions.

T. M.

ADVANCES IN INTERNAL MEDICINE, VOL. I, 1942. New York Number. Editor, J. MURRAY STEELE, M.D., Welfare Hospital, New York University Division, Welfare Island, N. Y. Pp. 292; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, \$4.50.

THIS is the initial volume of a new series of medical publications, prepared under the supervision of Dr. J. Murray Steele, as editor, and a group of highly qualified associates, consisting of Drs. William Dock, Tinsley R. Harrison, Chester S. Keefer, Robert F. Loeb, Warfield T. Longcope, George R. Minot, and I. Snapper. Each of the 10 presentations covers about 30 pages and consists of a review of a field of clinical medicine to which the author himself has made significant contributions and which is regarded as representing an advance in knowledge. The book affords the author an opportunity to present at greater length and more informally than can be done in an ordinary journal his personal viewpoint about his special subject. A list of the authors and the titles of their presentations is sufficient to indicate the character and importance of this first volume. The use of the Miller-Abbott tube in diagnosis and treatment is covered by W. Osler Abbott; use of insulin and protamine insulin in diabetes, by Paul Levietes; sympathetic nervous control of the peripheral vascular system, by Robert W. Wilkins; the antibacterial action of the sulfanilamide drugs, by Colin M. MacLeod; the choice of the sulfonamides in treatment, by Chester S. Keefer; infections of the urinary tract, by Lowell A. Rantz; epidemic influenza, by Thomas Francis; hypertension, by Irvine H. Page; nephrosis, by Lee E. Farr; and riboflavin deficiency, by Harold Jeghers.

Whether or not the medical public will support and profit by such a publication remains to be seen, but at least this volume, because of the choice of authors and subjects and because of the care with which the papers have been prepared, including in each instance an extensive bibliography, deserves the attention of all those who are making an effort to keep themselves informed about the advances in the broader field of clinical medicine.

T. M.

MICROBIOLOGY AND MAN. By JORGEN BIRKELAND, PH.D., Assistant Professor of Bacteriology, Ohio State University, Columbus, Ohio. Pp. 478; 35 figures, 9 charts. Baltimore: Williams & Wilkins Company, 1942. Price, \$4.00.

THIS book is designed as an elementary text for the student who plans to take but one or two courses in microbiology. It is intended to serve as a basis for an understanding of the part played by microorganisms in everyday life. It is a guide for learning as well as a source book of facts. Part I (130 pages) is devoted to the fundamentals of microbiology. Part II (48 pages) is a very brief discussion of infection and resistance. Part III (184 pages) is devoted to a discussion of specific infectious diseases. Diseases caused by bacteria, rickettsiae, and filterable viruses are included in the discussion, but not those diseases caused by animal parasites or fungi. An unfortunate error occurs on page 235 where it is stated that diphtheria toxoid is prepared by treating diphtheria toxin with formalin or by precipitating with alum. The omission of the genus *Clostridium* is not so excusable. No mention is made of tetanus or gas gangrene. *Cl. botulinum* is described under food poisoning, *Cl. welchii* is briefly mentioned only as an anaërobic spore former which may be used as an indicator of pollution, and *Cl. butyricum* is mentioned in relation to nitrogen fixation. Even a discussion of the methods for growing microorganisms anaërobically is missing from the book. Part IV (76 pages) is a discussion of the microbiology of food, milk, water, sewage, and soils. The appendix consists of a summary of the classification of the Class Schizomycetes, a glossary of terms, and a list of selected references.

H. M.

OPHTHALMOLOGY AND OTOLARYNGOLOGY. *Military Surgical Manuals, II.* Prepared and edited by the Subcommittee on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 331; 51 figures. Philadelphia: W. B. Saunders Company, 1942. Price, \$4.00.

THIS is one of a series of 6 volumes known as the "Official Military Surgical Manuals." These manuals have been prepared and edited by the various subcommittees under the auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council, with the coöperation of the Surgeons-General of the U. S. Army and Navy.

The general purpose of these volumes is to acquaint the physicians in our armed forces with officially approved methods, techniques, and treatments. "Ophthalmology and Otolaryngology" succeeds in its effort to supply clear, practical, and authoritative information concerning diagnosis and treatment of specific conditions of the eye, ear, nose, and throat. Twenty-three outstanding authorities handle a tremendous amount of material facilely, briefly, and explicitly. The chapters are well defined, the information is clearly organized and edited, and the book is nicely illustrated.

Although the specialist will probably find this manual too condensed for his purposes, the Army and Navy physician should have little difficulty in using it profitably as a practical guide and reference. I. L.

WAR AND THE DOCTOR. ESSAYS ON THE IMMEDIATE TREATMENT OF WAR WOUNDS. Edited by J. M. MACKINTOSH, M.D., Chief Medical Officer of the Department of Health for Scotland. Pp. 135. Second Edition. Baltimore: William Wood & Co., 1942. Price, \$2.00.

As stated by the editor, this book is a monograph made up of a series of lectures delivered at the request of the Edinburgh branch of the British Medical Association. These lectures were given by men whose battle experience dated from the war of 1914-1918. It is lacking in the experience that has been derived from the present conflict. Shock and hemorrhage is discussed without any reference to blood plasma. The surgical sections do not include any of our present knowledge of the use of sulfanilamide compounds. This gives a sense of unreality to what is otherwise a fairly adequate discussion of the surgical problems arising from war. Its greatest lack is that it does not cover the medical problems as they actually have developed. J. H.

DISEASES OF THE LIVER, GALL BLADDER AND BILE DUCTS. By S. S. LICHTMAN, M.D., F.A.C.P., Adjunct Physician, Mount Sinai Hospital; Assistant in Post-Graduate Medical Instruction, University Extension, Columbia University, New York. Pp. 906; 122 illustrations. Philadelphia: Lea & Febiger, 1942. Price, \$11.00.

THIS textbook presents a review of much of the literature on the anatomy, physiology, and diseases of the liver and the biliary system. The arrangement of its contents is unusual in that the author begins with a discussion of the microanatomy of the hepatic lobule, then in the chapters on the functions of the liver, its exogenous poisons, its morbid anatomy, the symptomatology and etiology of its diseases and its functional tests, he discusses in detail many purely clinical problems which have to be reconsidered when finally (page 355) he takes up the specific hepatic diseases. In spite of a formal and helpful classification of the functional tests (page 252), he later confuses the matter by taking up various tests applicable to the blood under the heading of those applicable to the urine (bromsulphthalein for instance). He repeatedly uses the word "data" in the singular.

The discussion of clinical entities, including affections of the gall bladder and biliary ducts, is very complete, but makes unnecessary reference to much of the older literature; in the end the Reviewer is often left in doubt regarding the author's own viewpoint. Apparently he regards hepatitis only as a disease of the liver of unknown etiology, referring separately to the affections resulting from known agents, such as arsenic, phosphorus, chloroform, toxic jaundice. This is at variance with the usual custom. Many of the illustrations are excellent. The book will be found useful mainly as a book of reference.

T. M.

THE HOSPITAL CARE OF THE SURGICAL PATIENT. By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic; and FRANKLIN L. SHIVELY, JR., M.D., Assistant Surgeon, Cleveland Clinic. Pp. 184; 21 figures. Springfield, Ill.: Charles C Thomas, 1943. Price, \$2.50.

THIS small volume is an extremely valuable asset to anyone caring for surgical patients. It cannot be recommended too highly for the surgical interne and resident; it foresees his every problem and includes a practical discussion of the procedures and complications arising every day in the hospital management of patients subjected to surgery.

The first section deals with the physiologic principles of water and chemical balance related to the care of the patient before and after operation. The second section is an admirable discussion of the management of post-operative complications. An acceptable, standardized technique for routine hospital procedures is presented in the third section. In each instance, care is taken to point out limitations and dangers as well as the actual indications. All who wish to keep in touch with the newer procedures employed to make an operation safe will find this book invaluable.

L. S.

MENTAL HEALTH IN COLLEGE. By CLEMENTS C. FRY, M.D., Lecturer in Psychiatry and Mental Hygiene and Psychiatrist to the Department of University Health, Yale University; with the collaboration of EDNA G. ROSTOW, Research Assistant in Psychiatry and Mental Hygiene, Division of College Psychiatry and Mental Hygiene, Yale University. Pp. 384. New York: Commonwealth Fund, 1942. Price, \$2.00.

THIS is a descriptive analysis of adjustment problems in Yale students treated during a 10-year period by the Division of College Psychiatry and Mental Hygiene.

The materials are drawn from case studies and are presented in case study form. Cases used represent varying degrees of maladjustment arising from a wide variety of causes and conditions. Procedures in treatment are outlined and results reported in those cases in which follow-up was made. Cases with certain common characteristics are grouped together and discussed. The authors emphasize, however, that the causes of a given adjustment problem are almost invariably complex and interactive, and that each problem must be studied individually, rather than treated as a "type."

Certain causal elements appearing frequently in the student cases grow out of (1) family relationships, (2) worries related to sex, and (3) parental or social "pressure for success."

The book does not contain explicit suggestions concerning improvement of the college environment to the end of reducing the incidence of mental ill-health. There are, however, many implications which should be noted by all readers who have responsibility for mental health conservation in college students.

T. M.

FAMILIAL NON-REAGINIC FOOD ALLERGY. By ARTHUR F. COCA, M.D., Medical Director, Lederle Laboratories. Pp. 160; 20 tables, 12 charts. Springfield, Ill.: Charles C Thomas, 1943. Price, \$3.00.

THE author presents very concisely a new method of approach to the diagnosis and treatment of a relatively large group of allergic diseases (migraine, urticaria, gastro-intestinal allergy, neuralgias, and a number of more or less serious conditions hitherto usually not recognized as allergic such as canker sores, constipation, nervousness, physical tiredness, chronic rhinitis, epileptiform seizures, even some cases of hypertension, and others). No implication is made that the above conditions are always allergic in origin, but by rather definite signs and symptoms he is able to select those that are. A surprisingly high incidence in these conditions has by the author's criteria of diagnosis been found to be of allergic origin, and accordingly the therapeutic test usually confirmed it.

The category of allergic disease designated as familial non-reaginic food-allergy is identified by the following points: Its characteristic symptomatology, the failure of the usual cutaneous tests, a separate hereditary influence, and the regular effect of an acceleration in the pulse rate. The author reports that without exception in the first 44 cases who completed the course of dietary treatment, when the pulse rate had reached the level and range that was recognized as normal for the individual, the chief symptoms completely disappeared.

Within this brief monograph are reported detailed methods of diagnosis and treatment with results in this type of allergy, and a discussion concerning the nature of this disease process. To the Reviewer the contents of this book seem to offer great hope and encouragement for the better identification and management of a significant number of common yet frequently distressing conditions seen by the clinician. A more extensive trial of the procedure described is needed, and the reported results would seem only to hasten this.

M. T.

CARCINOMA OF THE STOMACH. By WALTMAN WALTERS, B.S., M.D., M.S. in Surgery, D.Sc., F.A.C.S., Surgeon, Mayo Clinic; Professor of Surgery, University of Minnesota (Mayo Foundation); Commander, Medical Corps, United States Naval Reserve; Diplomate of the American Board of Surgery; Member, National Advisory Cancer Council; HOWARD K. GRAY, B.S., M.D., M.S. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; Associate Professor of Surgery, University of Minnesota (Mayo Foundation); Lieutenant Commander, Medical Corps, United States Naval Reserve; Diplomate of the American Board of Surgery; and JAMES T. PRIESTLEY, B.A., M.D., M.S. in Experimental Surgery, Ph.D. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; Associate Professor of Surgery, University of Minnesota (Mayo Foundation); Major, Medical Reserve Corps, United States Army; Diplomate of the American Board of Surgery; and Associates in the Mayo Clinic and Mayo Foundation, Rochester, Minn. Pp. 576; 152 figures and 82 tables. Philadelphia and London: W. B. Saunders Company, 1942. Price, \$8.50.

This monograph is the result of an analysis made on 10,890 cases in which the diagnosis of carcinoma of the stomach was made at the Mayo Clinic between the years 1907 and 1938, inclusive. Concerning its contents, the following can be copied without reservation from the authors' preface: "This book contains a thorough review of malignant lesions of the stomach by the authors and their associates at the Mayo Clinic. These chapters have to do with roentgenographic diagnosis, gastroscopy, the clinical features of malignant lesions of the stomach, the indications for treatment, and the nutritional deficiencies associated with such lesions. There is a

long chapter on preoperative treatment, selection of the anesthetic for a particular patient and a detailed presentation of the various types of surgical technic employed in the extirpation of malignant gastric lesions. The pathologic considerations are presented in two chapters, one by Dr. A. C. Broders and one by Dr. W. C. MacCarty. The postoperative treatment is thoroughly covered. Estimation of prognosis and end-results is accurate because of the very high percentage of follow-up studies that were made and calculation of survival rates covers periods up to twenty-five years subsequent to operation. There is a chapter dealing with roentgenologic treatment of inoperable lesions and a chapter on the operating room set-up from the standpoint of the surgical nurse." This the authors have well accomplished with resort to rather frequent statistical tabulations. The reader is spared academic considerations, and the observations and results are confined to the significantly large number of case records accumulated at that one place. One apparent typographical error is found (p. 108, l. 10)—the second word should read "microcytic" instead of "macrocytic." Although the book is limited to carcinoma (and other malignant neoplasms) of the stomach, the career of the gastric neoplasm is long and pertinent to many of the fields of medicine, so that the usefulness of this book immediately becomes great.

M. T.

NEW BOOKS

Diseases of the Breast. By CHARLES F. GESCHICKTER, M.A., M.D., Lieut. Comm., Medical Corps, U. S. Naval Reserve, Director of The Francis P. Garvan Cancer Research Laboratory, Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in Collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School, Visiting Surgeon and Assistant Oncologist, University Hospital, University of Maryland Medical School. Pp. 829; 593 illustrations. Philadelphia: J. B. Lippincott Company, 1943. Price, \$10.00.

Pancreatic Function and Pancreatic Disease Studied by Means of Secretion. By HENRIK O. LAGERLOF, M.D. Translated by HELEN D. DREY. With a Foreword by JOSEPH H. PRATT, M.D. Pp. 289; 50 tables. Printed in Sweden. New York: The Macmillan Company, 1942. Price, \$3.50.

Symposium on Office Gynecology. Medical Clinics of North America. Vol. 27, No. 1 (Chicago No.). Pp. 272; 19 figures and tables. Philadelphia: W. B. Saunders Company, 1943. Published bi-monthly. Yearly subscription, paper, \$12.00; cloth, \$16.00.

Essentials of Gynecology. By WILLARD R. COOKE, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Texas. Pp. 474; 197 illustrations, including 10 in color. Philadelphia: J. B. Lippincott Company, 1943. Price, \$6.50.

Burns, Shock, Wound Healing and Vascular Injuries. Military Surgical Manuals V. Prepared under the Auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 272; 20 figures. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$2.50.

The Vertebrate Eye. By GORDON LYNN WALLS, Research Associate in Ophthalmology, Wayne University College of Medicine. Pp. 785; 197 figures (3 in color); plates and tables. Bloomfield Hills, Mich.: Cranbrook Institute of Science, 1942. Price, \$6.50.

The Sight Saver. By C. J. GERLING. Pp. 202, frontispiece. New York: Harvest House, 1943. Price, \$2.00.

Treatment of Fractures. By GUY A. CALDWELL, M.D., F.A.C.S., Professor of Orthopedic Surgery, Tulane University of Louisiana School of Medicine; Senior Visiting Orthopedic Surgeon, Touro Infirmary; Visiting Surgeon, Charity Hospital of Louisiana; Director, Section on Bone and Joint Surgery, Ochsner Clinic, New Orleans. Pp. 303; 92 illustrations. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1943. Price, \$5.00.

This little book presents the treatment of fractures in a clear, concise and practical manner. It is well illustrated with line drawings, most of which are original. The recognition of shock and its most modern treatment thereof is also presented. Those appliances, splints and methods of treatment which have proven their value in many hands, are given preference. An excellent chapter on the treatment of compound fractures is given in minute detail, with particular mention of military conditions, débridement, chemotherapy and transportation. The use of pins and other means of internal fixation are described and recommendations given for their usage.

The author has given his readers a nice, complete, up-to-date and practical view of the treatment of fractures as met by the first aid or the medical attendant under civil and military conditions. E. E.

The Metabolic Cost of Maintaining a Standing Position. By HARRIET GRAHAM MCCORMICK, Associate in Physical Education, Teachers College, Columbia University. Pp. 84; 8 figures. Morningside Heights, N. Y.: King's Crown Press, 1942. Price, \$1.25.

The subject matter contains the methods used, calculations, and resulting implications obtained on 50 healthy adult subjects from a study designed to reveal any existing relationship between posture and the variation in metabolic increase in the standing rate over the basal rate, and how body alignment varies with any such existing relationships. Her results reveal that "for the normal, healthy individual of average height and weight, it would seem to make very little difference, as far as energy expenditure alone is concerned, what body alignment he assumes in standing." The detailed study will interest and serve all who are concerned with the basic problem or with the related one of helping individuals to improve their body mechanics and posture. M. T.

The Antigonadotropic Factor. By BERNHARD ZONDEK and FELIX SULMAN, Hebrew University, Jerusalem. Pp. 185; 23 tables. Baltimore: The Williams & Wilkins Company, 1942. Price, \$3.00.

This is a systematic alignment of opposing points of view on the nature of "antihormones", or substances responsible for the refractoriness which develops in animals as a result of repeated injections of certain hormones, particularly the gonadotropins.

The literature is extensively reviewed, and unpublished experiments of the authors are included. It deals largely with the immunologic and chemical principles involved in this particular phase of endocrine research. I. Z.

Emotions and Memory. By DAVID RAPAPORT, Ph.D., Head of the Department of Psychology, The Menninger Clinic. Pp. 282. Baltimore: The Williams & Wilkins Company, 1942. Price, \$3.00.

Renal Lithiasis. By CHARLES C. HIGGINS, M.D., Cleveland Clinic, Cleveland. Pp. 140; 18 figures. Springfield, Ill.: Charles C Thomas, 1943. Price, \$3.00.

A Surgeon's Fight to Rebuild Men. An Autobiography. By FRED H. ALBEE, M.D., F.A.C.S., F.I.C.S.; Foreword by LOWELL THOMAS. Pp. 349; 11 illustrations. New York: E. P. Dutton & Co., Inc., 1943. Price, \$3.50.

Food Poisoning. By G. M. DACK, Ph.D., M.D., Associate Professor of Bacteriology, University of Chicago. Pp. 138; 13 tables. Chicago: The University of Chicago Press, 1943. Price, \$2.00.

Bronchiectasis. By JAMES R. LISA, B.S., M.D., Pathologist, City Hospital, Welfare Island, Midtown Hospital, French Hospital, New York; and MILTON B. ROSENBLATT, B.S., M.D., Associate Visiting Physician, City Hospital, Welfare Island, Chief of Medical Clinics and Chief of Chest Clinic, City Hospital Division, Welfare Island Dispensary; Associate Attending Physician in Pulmonary Diseases, Montefiore Hospital. Pp. 190; 35 figures and tables. New York: Oxford University Press, 1943. Price, \$4.00.

NEW EDITIONS

Fractures. By PAUL B. MAGNUSON, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School, Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Pp. 511; 317 illustrations. Fourth Edition. Philadelphia: J. B. Lippincott Company, 1943. Price, \$5.50.

This edition maintains the excellent standard of the preceding ones. It further discusses the all-important questions of shock in its various forms and the treatment and handling of fractures under military conditions, with especial emphasis on débridement, chemotherapy and fixation. The use and abuse of plating and the various materials used in their making is considered in all phases. With the exception of some neglect in the index of the volume, the book ranks among those of other authorities on the subject. Furthermore, it is nicely bound, printed and indited. E. E.

The Relation of Certain Anomalies of Vision and Lateral Dominance to Reading Disability. By PHILIP W. JOHNSTON. Monographs of the Society for Research in Child Development. Vol. VII, Serial No. 32, No. 2. Pp. 153; many tables and figures. Published by Society for Research in Child Development, National Research Council, Washington, D. C., 1942. Price, \$1.50.

It takes 147 pages of statistics to prove that "any observed association between anomalies of dominance and reading disability in the case of children born between the dates of October 1, 1926, and May 31, 1937, and attending the Public Schools of Reading, Mass., can be explained on the basis of fluctuations due to the operation of chance factors." Doubtless such information has to be obtained, but it is somewhat like analyzing the rat's tail for arsenic for the reason that it has never been done before. F. A.

Medical Jurisprudence and Toxicology. By JOHN GLAISTER, M.D., D.Sc., Fellow of the Royal Faculty of Physicians and Surgeons, Glasgow; of the Inner Temple, Barrister-at-Law, etc., Regius Professor of Forensic Medicine, University of Glasgow; formerly Professor of Forensic Medicine, University of Egypt, Cairo; and Medico-Legal Consultant to the Egyptian Government. Pp. 671; 132 illustrations. Seventh Edition. Baltimore: The Williams & Wilkins Company, 1942. Price, \$8.00.

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON, M.D., Director of Laboratories and Pathologist, Research and Educational Hospitals, Chicago, Ill.; Professor of Pathology and Assistant Professor of Medicine, University of Illinois College of Medicine; and ROBERT P. MACFATE, Ch.E., M.S., Ph.D.; Assistant Director of Laboratories, Research and Educational Hospitals, Chicago, Ill.; Assistant Professor of Pathology, University of Illinois College of Medicine. Pp. 980; 156 illustrations, 15 plates (7 in color). Second Edition. Philadelphia: Lea & Febiger, 1943. Price, \$10.00.

Obstetrical Practice. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 938; 1064 figures. Third Edition. Baltimore: The Williams & Wilkins Company, 1942. Price, \$7.00.

This volume needs no introduction to teachers of obstetrics. The section on operative obstetrics has been completely revised and rewritten. The number of illustrations has been increased and some are in color. The volume is characterized chiefly by its numerous and excellent illustrations, especially those which deal with the mechanism of labor. Since its second edition appeared, one has been published in Portuguese. It is supplied with an unusually full index. For the practitioner the volume may be considered somewhat elementary, but for the medical student, anxious to grasp the subject with the least effort, it would seem that there could be no better choice. D. M.

Diseases of the Skin. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology, University of Illinois; Attending Dermatologist to the Presbyterian Hospital of Chicago; and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 1360; 654 figures (6 colored plates). Sixth Edition. Philadelphia, Lea & Febiger, 1943. Price, \$14.00.

PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

NOAH D. FABRICANT, M.D.

ASSOCIATE, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS COLLEGE
OF MEDICINE, CHICAGO, ILLINOIS

THE SURGICAL TREATMENT OF OTOSCLEROSIS

WITHIN the past few years the otologic world has become deeply interested in the surgical treatment of otosclerosis. The fact that the medical treatment of otosclerosis gave disappointing results stimulated a few intrepid surgeons to work on the problem of the surgical relief of otosclerosis. The early pioneers believed that they obtained an instantaneous improvement in hearing as soon as a fistula into the labyrinth was established. This was first observed in 1876 when Kessel extracted the ankylosed stapes and again in 1897 when Passow made a sound-fistula into the promontory with a trephine. There was little improvement in hearing, however, and it lasted but a few days.

General opposition to the operations arose, for they were regarded as dangerous to the hearing as well as to the life of the patient. For 10 years the problem slumbered, to be revived by Bárány who made a sound-fistula into the posterior vertical canal; but again, the improvement in hearing lasted but a few days. In 1913 Jenkins made a fistula into the horizontal canal and obtained immediate improvement in hearing in 2 cases of otosclerosis, but when one of the patients soon became completely deaf and the other lost the improved hearing, he abandoned the operation. Four years later Holmgren made a fistula on the upper curve of the anterior vertical canal, exposing this to the dura, and the immediate result was good but of brief duration. At this time Bárány made a fistula into the horizontal canal and covered it with a pad of fat previously transplanted into the mastoid cavity; an improvement in hearing was observed for 14 days. In 1920 Holmgren, employing magnifying optical instruments, made an opening into the promontory which he covered with mucoperiosteum, but again the result was only temporary. Two years later he utilized the same technique on the horizontal semicircular canal, with permanent improvement in hearing in some cases, although the improvement was never great. In 1924 Sourdille began working on the problem, and encouraged by his enthusiasm, results and technical skill, Holmgren further refined his technique. He exposed the saccus endolymphaticus and made a fistula into the horizontal and vertical semicircular canals. A prosthesis

of fat was placed over the fistula, the inner antrum wall having first been covered with gold leaf to prevent adhesion to the membranous labyrinth. In 1936 Holmgren⁷ described 34 patients who had been operated upon with different modifications of this technique. There were no serious complications and no deaths; tinnitus disappeared entirely or almost entirely, vertigo within a month, and the improvement in hearing was constant and surprising.

The technique of the modern exponents of the surgical approach to the otosclerosis problem was adapted and elaborated upon with considerable skill by Lempert.^{9a} He describes a procedure designed to create a fenestra in the bony capsule of the external semicircular canal and to provide a mechanical means of keeping the fenestra permanently open. Success depends on skilful and patient execution of a number of orderly surgical steps and its technique should not be attempted by any but otologists who have been specially trained to perform difficult surgical measures of this type. Indications for the operation are: clinical evidence of fixation of the stapes; loss of hearing by air conduction of not more than 60% (if practical improvement in hearing sufficient to permit the patient to resume his economic and social life is to be obtained); loss of hearing by air conduction of not less than 40%, when accompanied with a loss of practical hearing; normal hearing by bone conduction determined by masking or a loss in hearing by bone conduction, determined by masking, which does not exceed 30 decibels for the 512, 1024 and 2048 frequencies; complete absence of suppuration from the middle ear; completely normal and translucent membrana tympani without perforations; completely intact and healthy cutaneous lining of the bony wall of the external auditory canal; and a normal state of health. The endaural, antauricular approach to the temporal bone is employed because of the following reasons: the tympanomeatal cutaneous membrane can be obtained only when this approach to the temporal bone is used. To avoid risk of postoperative infection, in addition to applying the strictest rules of asepsis, the surgical attack must be limited to the tissues directly concerned and thus reach the objective with the least amount of sacrifice of tissue. Better visibility and accessibility of the desired surgical field are obtained by this approach. Lempert operated on 23 patients and in 19 good practical improvement in hearing was obtained and maintained; in 4 in whom the operation was performed despite poor existing bone conduction, no improvement in hearing was secured. The new fistula in the external semicircular canal remained open in 22 patients.

In 1940 Lempert^{9b} reviewed his results in 120 cases in which the operation was performed by means of his one-stage technique. The essentials of this technique are: creation of a new window in the horizontal semicircular canal to replace the occluded oval window, and reconstruction of the tympanic cavity to include within it this new window by: *a*, creation of an intact continuous membrane of the skin of the external canal, Shrapnell's membrane and the drum membrane; *b*, amputation of the head and neck of the malleus, to permit Shrapnell's membrane to be pulled back to cover the new window; *c*, preservation of the incus in its normal position; *d*, removal of the pyramidal eminence to widen the tympanic cavity; and, *e*, closing the tympanic

cavity from the outer ear with the tympanomeatal membrane so as to include the new window in the tympanic cavity. In the series of 120 cases, restoration of practical physiologic hearing occurred in 69 cases, marked improvement in conversational hearing in 10 individuals, no improvement in 27, and further loss of hearing in 14 cases. Tinnitus was completely relieved in 69 patients and was diminished in 10. In 100 of the 120 cases the new window remained open; in 31, revisions were done. In commenting on Lempert's work, Shambaugh^{13a} states that Lempert is criticized, partly by those who have not taken the trouble to investigate and observe his work and who have perhaps seen one or two poor results, since patients with poor results are more prone to seek help from other physicians than are those with good results. Others criticize Lempert because of his enthusiasm for his operation. For example, he uses the term "permanent improvement" when one cannot yet be sure of the ultimate fate of the hearing in the cases in which his technique has been used, since insufficient time has elapsed. Exception can also be taken to certain statements, *i. e.*, that Shrapnell's membrane reaches and covers the fistula and that infection of the outer middle or inner ear was never encountered. Shambaugh believes that a slight low-grade infection of the postoperative cavity must be a common occurrence and that Shrapnell's membrane does not cover the fistula. His experience with tinnitus has been less favorable. In some patients with excellent and sustained hearing improvement the tinnitus has recurred, and in others it has not been relieved. In other respects his experiences with the fenestration operation are similar to those of Lempert. From his experiences Campbell¹ believes permanent improvement of hearing in cases of chronic progressive deafness by fistulization of the labyrinth depends on maintenance of the fistula by prevention of bony regeneration of the labyrinthine wall. He reports on 8 cases in which fistulization was performed according to the technique described by Lempert. In 4, considerable improvement of hearing was shown by audiometric examination. In 2, hearing in the ear operated on had been made worse, and in the remaining 2 there was little or no change in hearing. Passe¹⁴ operated on 14 patients and finds that within 18 months following the procedure it is difficult to assess the real value of the operation. Though hearing showed improvement in 5 patients, only 3 have improved to an appreciable extent for conversation. In all but 5 cases hearing loss progressed after operation, but this loss was always more evident in the unoperated ear than in the operated ear. In all improved cases the fistula sign was present. In the absence of other treatment, Passe believes that these results justify continuance of efforts to produce a permanent opening in the bony canal. The indications for fistulization of the labyrinth are reviewed by Canfield² who presents 3 cases, 1 of a patient considered suitable for operation and 2 regarded as unsuitable. Of the latter, 1 had headaches of long-standing duration and undetermined origin, and the other had a healed cavity following radical mastoidectomy for chronic suppurative otitis media. The 2 unsuitable patients showed no improvement in hearing. The suitable patient showed an average gain of 15 decibels for the 3 conversational frequencies 1 month after operation.

In the opinion of Fowler^{15a} fenestration of the labyrinth is the one

surgical technique which appears promising for the alleviation of conduction deafness. On the basis of experimental work by himself and others he discusses the causes of closure of labyrinthine fistulas. The first factor is bone chips which act as foci from which new bone growth takes place. Second, it has been found that the enchondral bone of the labyrinthine capsule does not participate in the bony healing of fractures. Consequently, the fistula should be made in the solid angle where the enchondral capsule is relatively thick and the periosteal capsule is relatively thin. Third, a larger fistula is apparently less likely to close. Fourth, infection undoubtedly tends to increase bone regeneration. Finally, he expresses the belief that fistulization is as dangerous as any major surgical procedure on the mastoid, perhaps more so. Goodyear⁵ describes a simplification of the Lempert fenestration technique in which the conventional postauricular approach is employed. The operation was used on a patient who showed a positive reaction to the fistula test $3\frac{1}{2}$ months after operation. Utilizing the postauricular approach, Porta¹² makes a fistula into the horizontal semicircular canal, exposing the membranous canal widely and covering the fistula with a portion of the aponeurosis of the temporal muscle. An opening is then made into the external auditory meatus to this aponeurosis. The middle ear remains unopened. Because the fistula in the labyrinth frequently closes, improvement in hearing is often transient. Nasiell¹⁰ states that it is impossible to separate otosclerosis from chronic adhesive deafness, an artificial fistula being of equal importance in both diseases. Hughson^{8a} describes the indications for his round window graft operation for deafness. It is a procedure unsuitable for patients with hearing losses below the general level of 50 decibels, and should not be performed on patients over 50 years. Hughson and Witting^{8b} state that in view of the expected range of variation no change in the hearing level of any frequency less than 10 decibels can be considered of consequence. Because the 5-year cure has become more or less a standard for determining a satisfactory end-result in the majority of pathologic conditions, they maintain that a patient should have the assurance of retaining any gain obtained for at least this length of time. After presenting his results with his round window graft operation in a series of 30 patients operated on over a 3-year period, Hughson^{8c} concludes that his statistical analysis indicates a trend toward improvement in the patients on whom he operated. Subjective improvement was experienced by 60 % of all the patients and by 85 % of those with favorable results. Tinnitus was alleviated in 5 out of 15 patients, and in 1 patient it was worse. As a result of this surgical procedure in no patient was the hearing impaired.

Guggenheim and Guggenheim⁶ criticize the fenestration operation on three grounds. They state that the proponents of the fistula operation do not recognize the fact that otosclerosis is not only an osseous dystrophy producing an obstruction to sound conduction but that it is also a disease of the eighth nerve producing perception deafness, so that even though a fistula operation should prove successful, it could in no way inhibit further deterioration of the neural mechanism. They believe that medical treatment of otosclerosis through dietary regulation and the administration of calcium, phosphorus and vitamins has

produced improvement in hearing far greater than any fistula operation thus far reported. Finally, they maintain that the ingenious, difficult and time-consuming technique which has produced coast-to-coast enthusiasm has nothing whatever to do with the success or failure of the fistula operation. In an osseous fistula produced on rabbits, there was, after 18 days, lively and widespread new bone formation when the fistula was made with a sharp instrument or with a burnishing burr. No evidence of osteogenesis is detected at this time when the use of the burnishing burr has been followed by osteodesiccation by means of electrocoagulation. At the end of some 2 months, all osteoblastic activity has ceased and all mesenchyme has been replaced either by fatty marrow with islands of blood-forming cells or by fibrous marrow. The most patent fistula results from the use of a sharp instrument. Next came the fistula made with the burnishing burr and completed by electrocoagulation, while that made with the burnishing burr alone showed the largest amount of new bone formation. The fact that these operations were performed on a type of bone different from that of the labyrinthine capsule in no way affects the experiments, since all new bone formation is by the membrane-bone process. Shambaugh^{12b} takes issue with certain statements made by the Guggenheims relative to the fenestration operation for otosclerosis, namely that greater improvements have been secured by dietary management and that the difficult surgical technique has nothing to do with the end-results of the operation. Pointing out that no treatment for deafness can be regarded as of proved value until audiometrically substantiated and sustained hearing improvements of more than 10 decibels for the conversational frequencies are reported and that such improvements have never been reported following any medical or surgical treatment except for the fenestration operation, the author then presents his results in 31 cases of otosclerosis in which he operated by Lempert's fenestration technique. Of the 31 patients, 77% showed an audiometric improvement of more than 10 decibels for the conversational frequencies 3 weeks to 14 months after operation.

Ersner and Myers^{3a} find that the heat created by the dull dental burr during labyrinthine fenestration does not inhibit osteogenesis. It is believed that it is not the mechanics of the formation of a fenestra that baffles the otologist but the osteogenesis and closure of the fenestra that continue to present the perplexing problem. There is a macroscopic difference in the appearance of the bone after the fenestra is formed by the Holmgren method as compared with that of Lempert. The scraping method of the former leaves the bone dull, and the burring method of the latter leaves it shiny. Experimental work on cadavers and cats showed that the amount of heat produced in the bone by dental drills is slight. They conclude that although the difficulties attending the surgical treatment of otosclerosis have been overcome, the improvement of hearing of patients is only temporary in most cases. In another communication, Ersner and Myers^{3b} state that it is impossible to tell beforehand who will and who will not be benefited by the operative procedure. Despite care in determining that bone conduction was good, that evidence of neural involvement was lacking, that the labyrinth functioned normally and that hearing by air conduction was not

lost to the extent of more than 70 decibels, end-results have not been as good as the authors hoped to achieve. With regard to end-results, mere numerical improvement in decibels is of little value unless it brings the patient's hearing within conversational range. Unless this is achieved the operation must be considered a failure. According to Fowler,^{4a} recent reports are particularly open to criticism because of their optimistic conclusions and the paucity of facts supporting these conclusions. Outside of surgical methods for combating infection in the middle ear, there is only one surgical technique, fenestration of the perilymphatic labyrinth, which appears promising for alleviation of conduction deafness. Up to the time the article was written, reports complete enough to analyze show that in less than one-third of the cases in which operation was done satisfactory improvement was maintained for more than 6 months. To be legitimate, the minimum requirement for any elective operation for deafness should be an average improvement of at least 15 decibels for the speech range and a permanent reduction in hearing to 30 decibels or less. Elsewhere, Fowler^{4b} describes his experiences with closure of operative fenestras in the labyrinth.

A new oval window for improvement of hearing in cases of otosclerosis is described by Lempert.^{9c} After the performance of 375 fenestration operations and observation of the end-results, Lempert is convinced that fenestration of the labyrinth is indicated only when air conduction deafness has resulted from stapedial fixation and degeneration of the cochlear nerve has not yet produced impairment of the conversational frequencies, 512, 1024 and 2048. Desirable late end-results can be obtained in such cases only if there are normal and completely intact drum membranes, patent Eustachian tubes, and complete absence of middle ear infection. In 88 of 300 instances in which the external semicircular canal was fenestrated, the newly created fenestra eventually closed partially or completely. There was a period of 2 to 5 months before operation and closure. His study shows that a positive fistula test following fenestration indicates patency of the fenestra only when improvement in hearing continues. In cases of incomplete closure, the minute opening in the region of the ampulla may give a positive fistula reaction but is not sufficient to permit mobilization of the perilymph by air-borne sound and result in improved hearing. After covering the newly created fenestra with the tympanomeatal membrane in 50 cases, Lempert lifted the membrane and uncovered the fenestra after a 10-minute interval. Blood had entered the perilymph space and formed a fibrinous film in every case. This led him to consider the creation of a fenestra: first, in that part of the vestibular labyrinth which has the largest circumference of perilymph space and, second, in a position anterior to the ampulla of the external semicircular canal instead of posterior to it. Thus the fenestra would be nearer Shrapnell's membrane, which makes certain that Shrapnell's membrane always completely covers it. Accordingly, such a fenestra should be an unfavorable site for organization and conversion of a small accumulation of blood in the perilymph space into fibrous connective tissue, and thus its closure by bony metaplasia of a connective tissue mass should be prevented. In order to meet these requirements, the dome of the vestibule was chosen as the most suitable and advantageous

place for the creation of a new labyrinthine fenestra. The fenestra nov-ovalis was established in 75 cases in none of which did signs of impending closure of the fenestra exist at the time of the report. The comparatively large dimensions of the perilymphatic space in the region of the fenestra nov-ovalis offer an opportunity for inserting and permanently maintaining in direct contact with the lateral bony walls of the fenestra, an inert metal obturator frame (platinum and iridium) for mechanical prevention of closing of the fenestra. The observations indicate that fenestra nov-ovalis is anatomically well placed, histologically well constructed, and physiologically has a good functioning hearing window conceived and used to replace a functionally impeded fenestra ovalis. Like the fenestra ovalis, the fenestra nov-ovalis communicates directly with the scala vestibuli. Like the fenestra rotunda, it is covered by the thinnest possible membrane, both the inner and outer surface of which are lined with epithelium. According to Shambaugh,^{13c} the comparative merits of different surgical techniques for improving hearing in otosclerosis can be determined only by a comparison of the hearing results. The minimum data necessary for evaluation and comparison of results should include the following features: every operated case should be reported; hearing should be measured audiometrically; there should be adequate controls, the unoperated ear being the best control; at least 6 months should elapse before regarding a hearing result after fenestration as probably permanent; and all complications and untoward results, including dead labyrinthitis, should be recorded. All reports of the result of therapy for deafness should present these data. A comparative analysis of the results with four different surgical techniques for improving the hearing in otosclerosis showed that the original Lempert fenestration technique yielded a lasting significant hearing improvement in 27% of cases. The addition of constant irrigation to the technique resulted in a lasting significant hearing improvement in 76% of cases. The further addition of the binocular dissecting microscope to the technique resulted in a lasting hearing gain in 78% of cases. The nov-ovalis technique with irrigation and the microscope yielded a hearing gain in 88% of cases that have been tested 6 months or longer after operation.

NOAH D. FABRICANT, M.D.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.

HERMAN BEERMAN, M.D., AND NORMAN R. INGRAHAM, JR., M.D.

PROFESSOR AND ASSISTANT PROFESSORS, RESPECTIVELY, DEPARTMENT OF DERMATOLOGY
AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIAPINTA—A REVIEW OF RECENT ETIOLOGIC AND
CLINICAL STUDIES

WE have a fourfold purpose in reviewing the newer developments in the knowledge of pinta. Although there are several excellent reviews in English by Sáenz, Grau Triana and Alfonso Armenteros,^{68a} by Pardo-Castello and Ferrer⁶⁰ and by Holcomb⁴⁰ and numerous papers by various Latin Americans and a monograph by León y Blanco,^{49ff} these accounts are not readily accessible to the majority of the medical public. Pinta deserves special attention and repeated emphasis at this time because of the numbers of military personnel who are stationed, or will be, in the tropics. Certainly after the war it may be expected that cases of it will turn up in this country. Furthermore, it is a medical condition involving large numbers of people and recent years have added much to our understanding of its etiologic and clinical background. Finally, pinta is of great theoretical interest in that the recently discovered spirochetal (treponemal) cause for it further complicates the question of treponematoses by adding still another diseased state which has to be given a proper nosologic interpretation. It is our purpose, therefore, to discuss briefly the possible relation of pinta to other treponematoses and to present the data which comprise the present knowledge of the condition.

The Treponematoses. Although our experience has suggested the possibility of the existence of strains of *Spirochæta pallida* with individual biologic characteristics (c. g., treatment resistant^{7,8}), we are not proposing to discuss the treponematoses from the partisan viewpoint and side either with the unitarians or the dualists. For the sake of better understanding of pinta, however, a brief résumé of the arguments for and against the unitarian viewpoint is desirable. For a complete recent review of the subject the reader is referred to Goodman,³² Stannus,⁷¹ Blacklock,¹¹ Butler,¹⁵ Williams,⁷⁹ Fox,^{26f} Turner and associates (Ferris and Kumm^{24,45,75}), Hudson,⁴¹ Pardo-Castello,^{59b} Hoffman,³⁹ Hasselman³⁷ and others. Hudson (personal communication, as yet unpublished) has defined the treponematoses as, "a universally distributed acute and chronic specific disease, known in various times and places by a large number of names, such as syphilis, yaws, pinta, bubas, button scurvy, morbus gallicus, bejel, morfea, pian, irkintji, franghi, mentagra, carate, frambesia, venereal leprosy, sibbens, empeynes, radesyge, and many others. It is caused by a treponema, and is propagated both venereally and non-venereally. It is susceptible to treatment with the heavy metals, is diagnosed by special tests, is characterized by an early and late stage separated by a latent period.

and it evokes a characteristic pathological response from human tissues."

The precise relationship of the individual members of this group to each other has not been definitely determined and for a number of generations physicians have claimed sufficient differences both clinical and epidemiologic for many of them to distinguish them by separate names. Others have presented clinical material which demonstrates that the differences are not real (mucous membrane lesions occur in yaws;³⁶ and bejel;^{41a} nervous system lesions are found in bejel;³⁸ bone lesions in yaws and in bejel;^{65,79} palmar and plantar lesions in bejel and in pinta, especially in the Cuban cases;^{41c,68a} juxta-articular nodules in bejel;^{41d} visceral and aortic changes in yaws and in pinta;⁷⁸ depigmentation in bejel;^{41c} as well as in pinta.)^{49e} The chief point of discussion is whether the dissimilarities claimed for the various members of the group are due to variations in the host or his environment or to inherent biologic differences in the infecting organisms. The immunologic relations between the conditions are not clear. Hudson, from his extensive study of bejel, believes that environmental factors (climate, sociologic, economic, religious, and medical) play a great rôle in determining whether the disease is transmitted venereally (syphilis) or non-venereally (bejel). On the other hand, while the dualists believe that there are biologic differences among the causative organisms of the treponematoses, they admit that perhaps in the remote past they were identical, but that there is no good evidence to indicate that differentiation occurred within historic times. Blacklock¹¹ and others (Hudson) have clearly pointed out that those who claim syphilis and yaws (also bejel and pinta) are different diseases are comparing a non-venereal disease of children (bejel) or of rural areas of the tropics (yaws) with adult venereal syphilis.

Definition. Pinta is a chronic endemic disease of long duration, infectious, possibly contagious or transmissible by an as yet unknown vector. It is characterized by papular or papule-like initial lesions and is followed in a variable but usually long time by an erythematous squamous eruption which increases continuously and is transformed into dermatitic plaques which are superficial atrophic, pigmented and achromic, accompanied frequently by palmar or plantar keratodermias, and enlargement of superficial lymph nodes. It is now supposed to be due to a specific treponema. The cutaneous lesions are at times accompanied by visceral changes (aorta, nervous system).

Synonyms for Pinta. Pinta has been known by a variety of names according to the locality in which it is described. Pinta resembles yaws and bejel in the multiplicity of designations used among native peoples for it. Long lists of recent and older local designations for the syndrome are given by Brumpt,^{14b,c} by Holcomb,⁴⁰ and by León y Blanco.^{49ff} The name, pinta, or *mal del pinto*, is said to have originated in Mexico and one of the first to use this name was the American physician, Samuel M'Clellan⁵³ in 1825. Among the more commonly used names are *Tiña*, *Mal del Pinto* (Mexico), *Carate* (Colombia), *Azul* (Chile, Peru), *Boussarole* (Haiti), *Guasarola* (Dominican Republic), *Purú-purú* (Brazil), and *Catini* (Guatemala).

History. León y Blanco^{49dd,ee,ff} reported an extensive study of the historical development of the knowledge of pinta. This full account

has been supplemented by contributions dealing with special aspects (Pequeño,^{62b,c} Holcomb,⁴⁰ González Herrejón *et al.*,^{30,31} and Sáenz, Grau Triana and Alfonso Armenteros^{63a}). Beginning with the report of Alzate y Ramírez,¹ the subsequent story of the sequence of events leading to the present concept of the syndrome is full of information which foreshadowed much that is now considered new. The reader is referred to the original studies for details but certain recent developments must be outlined. Little attention was paid to pinta until Ruiz Sandoval⁶⁶ and Montoya y Flores⁶⁶ described certain phases of it and expounded the parasitic theory, and considered a number of *Aspergilli* and *Penicillia* as the cause. For about 25 years subsequently, it was considered as a more or less rare tropical disease. The recent history of pinta has been divided by Sáenz and his associates^{68a} into three periods. The first period extended from 1921 to 1929 during which time the condition was considered to be a special type of late keratotic syphiloderma of the palms and soles. The second commenced in 1929, when this condition was presumably identified as carate, an advancement in which Dr. Howard Fox²⁶ of New York, and Peña Chavarria and Shipley,⁶¹ played a prominent part. The third period began August 3, 1938, with the discovery of the spirochete which causes the condition, in dyschromic lesions and lymph nodes, and with the confirmation of the hypothesis previously held by certain investigators as to the spirochetic nature of the disease.^{26,31,54}

Geographic Distribution. Frequency of Occurrence. Pinta is almost entirely American in distribution. It affects chiefly dark-skinned peoples and is endemic in Colombia and Mexico. It also occurs in Venezuela, Cuba,^{35,59a,60,63a} Brazil,⁷⁰ Ecuador,^{22,48} Peru, Bolivia, Guiana, Honduras, Argentine, Nicaragua, Puerto Rico,¹⁶ Haiti,³ Santo Domingo, Virgin Islands,^{26h} Guadeloupe, San Salvador,^{5,61} and Central America (Panama). The Puerto Rican cases are said to occur in immigrants from Colombia. No cases apparently have been reported from Uruguay. Fox^{26c} could not confirm the reports that white pinta or vitiligo existed in Yucatan.

Cases of pinta have been reported from other parts of the world. Africa,¹⁰ Egypt,⁵² Algiers,³³ Sahara,⁴³ east of Tripoli,⁴⁷ Turkestan, Philippine Islands,⁸⁰ and Turkish Isles in the South Pacific. Cases have also been reported from Iraq and among the dark-skinned races of India,^{21,51} and the Straits Settlements.^{21,51} Fernandes²³ and DeSilva²⁰ reported on pinta occurring in Ceylon. Fox^{26d} claimed that the case reported as pinta by DeSilva²⁰ was unproven.

About 1,000,000 persons in Latin America are affected by pinta. Of this number about 300,000 cases are in Mexico, 600,000 are in Colombia. Iriarte⁴⁴ estimated that there were about 400,000 cases in Colombia, and about 55,000 cases in Venezuela. In Cuba where so much advancement in the knowledge of the disease has occurred, there are only about 200 cases.^{49ff} In Ecuador, there are approximately 5700 cases.

In Mexico, a commission found in 1929-31, 11 % of 2,500,000 people examined were affected by the disease. The disease is endemic in approximately the southern half of the Republic. The greatest number of cases were observed in the State of Guerrero, 23.67 % of the population of more than 500,000 being affected. Other states in which the disease was most prevalent were in order of frequency, Oaxaca, Mexico,

Michoacan, Puebla and Chiapas. In certain municipalities of the state of Barinas in Venezuela more than 50% of the inhabitants are affected and for the entire state the incidence is not less than 10%.¹³ Peña Chavarría and Shipley⁶¹ estimated that about 6.8% of the inhabitants of Colombia have the disease. León y Blanco^{49ff} cites other available data on the incidence of pinta.

Etiology. *Discovery of the Spirochetal (Treponemal) Cause of Pinta.* For about 45 years a parasitic cause was surmised for pinta. At one time, a bacillus was thought to be involved.²⁸ A mycotic origin was suggested by some of the earlier writers,^{4,56,66,67} and as late as 1936 Brumpt^{14a} listed 27 species of fungi reported to be the cause according to various authors. In 1889, Téllez⁷³ for the first time recorded the idea that pinta is an exanthematic form of syphilis and is transmitted by venereal contact. Although a number of investigators had failed to be satisfied with the mycotic origin of the disease,^{2,17,25,26} and in spite of the report of Gratz³⁵ and of Soberón y Parra⁶⁹ of the curative action of neosalvarsan, the possibility of a spirochetal cause of pinta was not given much consideration until the work of Menk⁵⁴ and González Herrejón.³⁰ Menk, of the United Fruit Company, studied 67 patients with carate in the Hospital Santa Marta in Colombia and found that 74.5% of them had a positive Wassermann reaction. He believed that these results indicated that carate is in some way related to an old treponematosi and that at least there is an association of etiologic factors such as a treponematosi and mycosis occurring at the same time. In 1927 González Herrejón came independently to the conclusion, after the intensive study of 3 cases, that pinta was not a mycosis but a spirochetosis related to syphilis and yaws. González Herrejón and Pallares³¹ found positive serologic reactions in nearly 100% of the patients suffering from pinta in Mexico, and were unable to isolate pathogenic fungi from the affected skin. Fox, in 1928^{56a} and 1930,^{26c} was unable to obtain pathogenic fungi from the skin of pinta patients and agreed with González Herrejón that the disease was a spirochetosis. In 1930 Thonnard-Neumann⁷⁴ and associates found 90% positive Wassermann reactions in their 75 cases. They also found positive cerebrospinal fluids in 2 of 5 cases and changes in the aorta, demonstrable roentgenologically, in 80% of the cases. Pardo-Castello in 1936^{59a} reported a number of cases of pinta from Cuba and affirmed the spirochetal nature of the disease in conformity with González Herrejón and Fox. Mooser, Varela and Vargas⁵⁷ did not find any organisms in the scrapings from lesions and the blood of Mexican patients with pinta and attempts to transmit the infection were unsuccessful. The positive proof of the spirochetal nature of pinta was developed when, on August 3, 1938, Drs. Grau Triana and Alfonso Armenteros, on the service of Prof. Braulio Sáenz, found a spirochete in the lymph of the dyschromic cutaneous lesions of a Cuban case of pinta. This spirochete was undistinguishable from that of syphilis and yaws. León y Blanco⁴⁹ found the organisms in the lymph nodes (juice of lymph node obtained by "gland puncture" and by Levaditi stain in sections. These findings were confirmed by Pardo-Castello⁶⁰ two days later in a case of his own in the dermatologic service of the Hospital Calixto GARCÍA. Because of the scarcity of cases in Cuba, León y Blanco was sent to Mexico where he made a number of important

studies which have changed the entire clinical concept of the disease. He demonstrated that the treponemas were present constantly in the cutaneous manifestations of the disease and absent in healthy persons. He also produced the disease experimentally in man, studied pintaginous zones in Mexico, established the course of the disease and various factors concerned with its epidemiology. His studies have been confirmed by various investigators in several of the Latin American countries.^{13,16,22,27,30,48,76}

The Spirochete (Treponeme). Various authorities have described the organism, presumably responsible for pinta. It has been variously called *Treponema carateum* (Brumpt), *Treponema herrejoni* (León y Blanco), *Treponema pictor* (Grau-Alfonso) (Pardo-Castello^{59a,c}), *Treponema americana* (Briceño Rossi and Iriarte), *Treponema diseromoderna* (Leon), *Treponema pintæ* (Sáenz, Grau Triana, and Alfonso Armenteros). It has been found in serum from keratotic lesions,^{49c,aa} in biopsy material from the skin lesions, especially the erythematous-squamous lesions ("empeines" or "jiotes" as they are called in Mexico). León y Blanco^{49aa} found the organism 254 times in 254 cases examined. They were first found in dyschromic and hyperkeratotic lesions of the hands and feet, typical of Cuban pinta.^{68a} In late lesions, the spirochetal findings are variable. Pardo-Castello and Ferrer⁶⁰ found them to be as rich in spirochetes as the early ones, but the active edges are usually more so. The atrophic areas ("burnt-out process") are usually free of spirochetes. The organism is morphologically indistinguishable from *Spirochæta pallida* and, except for minor variations, the description of León y Blanco^{49f} is widely accepted:

Dimensions of the organism. "The length varies greatly between 7.8 and 36.8 micra; it has been calculated an average value of 17.8 micra from 500 measurements, ranging in length from 12-18 micra ordinarily. It is from 0.25 to 0.30 micron thick and its spires are from 0.8 to 1 micron in depth, measuring the size of each interval of the screw 1 micron. The number of spires changes according to the length of the particular specimen observed.

"By darkfield examination it looks like a cylindrical filament rolled up around a fictitious longitudinal axis in the form of a helix or screw, the spires of which being very regular and close. Such spires appear rigid at rest, but they contract and relax constantly along the longitudinal axis of the screw whenever the germ moves. Its ends are sharp-pointed.

"The motility of *T. herrejoni* holds a very close resemblance with the motility of *T. pallidum*, showing as high a rate as that of the latter. It turns rapidly around its longitudinal axis and may exhibit an O, P, or S-shaped form after bending itself by distortion or flexion movements. Undulating or creeping movements are not infrequently shown by the whole body of this parasite.

"It is readily stained by the silver impregnation methods advised for staining Spirochetes in smear preparations, as well as by Giemsa's stain, Carbol-fuchsin, and Gentian Violet, after picric acid, tannin or Potassium permanganate has acted upon the smear.

"A 10% solution of Saponin dissolves these Treponemata in 6 hours at room temperature. The same result is obtained either by sodium taurocholate or bile. Distilled water causes them to swell."

León y Blanco has not yet succeeded in culturing the organism and a suitable animal for inoculation still remains undiscovered.

In fresh preparations the organism remains motile from 1 to 6 hours according to the temperature. Heating the specimen to 50° C. for 15 minutes kills the organisms but at 40° C. and at 42° C. they survive 3 and 1½ hours respectively. Varela and Nieto Roaro⁷⁶ found that the organism dies more quickly in bile than does *Spirochæta pallida*.

Curbello, Palomino, Conde and Garzon¹⁹ have cultured biopsy material from pinta lesions in ascitic fluid under aerobic and anaerobic conditions. They were able to produce a spirochetal keratitis by injecting this culture material into the anterior chamber of the eye of a rabbit. León y Blanco^{49f} was unable to confirm these findings.

Transmissibility of Pinta. Attempts to inoculate guinea pigs, rabbits and rats with pinta have failed.⁷⁷ Sáenz^{68b} stated without detail, that "the cornea and testicles of rabbits were inoculated with fragments of tissues from persons with pinta, and keratitis and epididymitis similar to those obtained in experimental syphilis resulted." Although Ortiz and Gandara⁵⁸ were able to produce keratitis by inoculating serum from skin lesions containing numerous spirochetes, no organisms could be demonstrated in the lesions thus induced. Attempts by the same investigators to produce lesions in parrots and pigeons were also unsuccessful.

In spite of the reported failure of Mooser, Varela and Vargas⁵⁷ to produce positive inoculation of healthy men and laboratory animals with the blood and exudates from the lesions of pinta, León y Blanco in 1938^{49c} successfully inoculated himself and volunteers with material containing the spirochete of pinta. As a result of these inoculations he has made observations which have clarified the clinical concepts of pinta. This investigator found, incidentally, that syphilis does not render a patient immune to pinta. A superimposed infection cannot be obtained during the pigmentary period of pinta; on the other hand, it is always obtained during the initial or spreading periods of the infection. A first attack does not give rise to immunity. A short time after recovery from the first attack (2 months after recovery from the disease in the primary period or 4 years in the dyschromic one, approximately) it is possible to produce experimental reinfection.

Aside from direct inoculation of infected material from a diseased to a healthy person, pinta is thought to be carried to the new host by way of an insect vector. This idea has been entertained for a long time. León y Blanco and Soberón y Parra⁵⁰ fed the fly *Mosca Hipelates* with serum containing *Treponema herrejoni* and succeeded in transmitting the disease by placing the flies to feed immediately afterward on cutaneous excoriations of a volunteer. León y Blanco^{49b} also found the treponemata of pinta in bed-bugs (*Cimex lectularius*). He believed that if the insect vector is involved, it might transmit the disease by depositing upon the abraded skin its feces containing the spirochete or by being crushed upon abraded skin at the time of biting.

The histologic changes in the cutaneous lesions and the lymph nodes in pinta have been fully described by León y Blanco.^{49g} The initial lesion and pintids show slightly thickened epidermis with elongation of the papillary processes. The stratum mucosum presents edema and intercellular infiltration of lymphocytes. The pigment is scarce in the basal layer. The corium shows a dense perivascular infiltrate of plasma cells, lymphocytes and occasional histiocytes and polymorphonuclear

leukocytes. There are numerous melanophores in the papillary layer. The endothelium of the blood-vessels are invaded and sometimes dissociated by the inflammatory cells. The pigmentary changes reflected by the blue-black or brown of the lesions are already noted in the histology of the early lesions.

The late lesions show "atrophy of the epidermis, absence of pigment in the basal layer, huge accumulation of melanophores in the upper part of the corium, alternate or continuous band-like infiltration of lymphocytes in the papillary and subpapillary layers, and, in cases in which the hyperkeratosis is a decided feature, the accumulation of corneous material on the atrophied epidermis."⁶⁰

In all cases studied by Pardo-Castello and Ferrer, "atrophy of the epidermis has been an almost constant feature and the patches of melanophores in the subpapillary region a characteristic histopathologic observation. Extracellular grains of pigment may also be noted in and between the cells of the infiltrate. In the leukodermic patches, there is complete absence of pigment, atrophy of the epidermis, disappearance of the papillæ and sclerosis of the connective tissue. These are evidently the end of the inflammatory process and represent the final stage, atrophic and cicatricial, of the disease. However, León y Blanco^{49ff} reported on some early vitiligoid lesions with active inflammation in which spirochetes are particularly abundant." Pardo-Castello and Ferrer⁶⁰ have been able to confirm this observation in a case of vitiligo-like lesions of the scrotum. Becker⁶ considered the depigmented spots of pinta as an end-stage, and hence its lack of response to treatment. In all lesions of pinta it is possible to demonstrate spirochetes among the cells of the epidermis, especially in the stratum Malpighii by silver impregnation methods.

Sáenz, Grau, Triana and Alfonso Armenteros⁶⁸ have described the essential pathologic features of keratosis. The chief epidermal change is marked hyperkeratosis. Otherwise the findings are essentially as outlined above.

León y Blanco^{49c} in his discussion of lymph node pathology noted that all are affected by chronic adenitis very much like that of syphilitic lymph nodes. The process terminates in a perivascular sclerosis and on spreading destroys almost all the parenchyma. Two features distinguishing pinta lymph nodes from syphilitic lymph nodes are the constant presence of melanin pigment and some hyaline corpuscles the nature and significance of which are as yet undetermined.

Eosinophilia. In 1925 Peña Chavarría and Shipley⁶¹ called attention to the occurrence of eosinophilia (10% to 73%) in pinta in patients free from intestinal parasites. These results were confirmed by González Herrejón (1927)³¹ and others. Eosinophilia occurs in about 75% of cases. León y Blanco also observed increase in basophils in 10% of cases. Local eosinophilia also occurs in the cutaneous lesions and enlarged lymph nodes of pinta.^{49bb}

Serology of Pinta. Two facts have been disclosed by numerous studies which indicate the relationship of pinta to syphilis. They are the blood-serologic findings and the response of pinta lesions to antisyphilitic remedies. The outcome of the blood tests and the results of treatment are well known to syphilologists to be highly non-specific in nature.⁷² Nonetheless they have played a prominent rôle in the

development of the spirochetal theory of etiology of pinta and will be briefly reviewed. The serologic tests are still of value in diagnosis, if not differential diagnosis, and the antisyphilitic therapy offers hope for control of the disease, pinta.

The blood serologic tests, both complement fixation and flocculation, have given variable but uniformly high percentages of positive reactions in the various phases of pinta. Pardo-Castello and Ferrer⁶⁰ in a summary statement believed the serologic reactions were positive in about 60 % of patients with the early stage of the disease. Serologic reactions in the late period of the disease were, according to these investigators, positive in 100 % of the cases. The serologic reactions gradually become positive as the disease evolves. Effective treatment usually has no influence on the serologic reactions. This serologic fastness is, according to León y Blanco⁴⁹ a constant feature of pinta (*secuela serologica*).

The proportion of positive serologic reactions in pinta varies according to the author, the type of test and the phase of pinta considered. Menk⁵⁴ found 74.5 % positive Wassermann reactions. Register⁶⁴ used the Wassermann, Kahn and Meinicke tests. Of 287 patients tested with the Wassermann test, there were 80.6 % strongly positive, 4.8 % moderately positive, 6.7 % negative, and the remainder negative. 117 of those tested with the Kahn test, 81.1 % gave positive reactions, 5.6 % were weakly positive and 7.6 % were negative. The Meinicke test gave 74 % of 118 cases positive, 5.4 % slightly positive, and 11.4 % negative.

Pérez Rodríguez⁵³ found the Wassermann test strongly positive in 95.5 % of 109 cases. Thonnard-Neumann and associates⁷⁴ found 90 % of 75 cases in Colombia positive. Briceño Rossi and Iriarte¹³ in Venezuela found that in two regions the treated cases gave 78 % and 77 % positive Kahn reactions, while among the untreated cases the percentage of positive Kahn reactions was 100. A Mexican Commission⁶⁵ found 125 of 130 cases positive. León in Ecuador found 78 % positive to the Wassermann test and 90 % positive Kahn reactions. The strength of the flocculation reactions was more intense than the complement fixation reactions. González Guzmán²⁹ in a series of 3 papers found that with the Wassermann and the Kahn verification tests the blood of pinta patients reacts like the blood of patients with syphilis. The verification test gave the syphilitic type of reaction in 20 patients with late clinical lesions. In patients with "pintides" (early stage) the Kahn test always gave positive reactions but the Wassermann test yielded inconstant reactions, being negative in 30 % of the cases. Chargin and Rein¹⁸ tested 268 cases of pinta with the Kahn verification test. All gave positive (4 to 160 units) reactions to the Kahn quantitative test. Of the 225 specimens, 83.9 % gave the syphilitic type of verification reaction while 6.3 % gave the general biologic (non-syphilitic) type of reaction, and 9.7 % gave inconclusive results. These data parallel those of Escobar. Briceño Rossi and Iriarte¹³ performed 111 Kahn verification tests in cases cured after 1 year. While the proportion increased to 100 % in the active cases, 78 % were strongly positive. Recently a new Kahn verification procedure has replaced the heat test. No reports have been found based on the application of this new procedure to pinta blood. Sáenz, Grau Triana and Alfonso Armenteros⁶³ found persistently positive serologic

reactions in all their cases in spite of treatment. León y Blanco^{49g,cc} studied the serologic reactions in various phases of pinta. In the primary period, he found negative reactions in 17 experimentally inoculated patients, at the time of inoculation and just at the start of treatment. In the secondary period, he performed 94 Bordet-Wassermann tests and 107 Kahn tests. While 88.78 % of the flocculation tests gave positive reactions, 86.14 % of the Bordet-Wassermann tests also gave positive reactions.

The cerebrospinal fluid in pinta has also received considerable attention. The Mexican Commission⁵⁵ found meningeal reactions and strongly positive Wassermann reactions. Varela could find no cerebrospinal fluid changes but in 1936 Pardo-Castello^{59a} in his study of 23 cases found 5 with increased globulin values and in 1, positive Wassermann and Kahn reactions. In his study with Ferrer, Pardo-Castello⁶⁰ reported that in 12 of 23 (52.1 %) cases examined there were pathologic changes in the cerebrospinal fluid similar to those found in asymptomatic neurosyphilis. Sáenz and his coworkers⁶⁸ found cerebrospinal fluid changes in 10 % of the cases. Grau Triana³⁵ studied the cerebrospinal fluid of 12 patients with pinta and found abnormalities in 2 of them. Botero¹² found no cerebrospinal fluid changes in 69 patients with earate examined. León y Blanco in unpublished work found no abnormalities in the cerebrospinal fluid of 53 patients in the late phase of the period of generalization.

Treatment. The treatment of pinta is similar to that of syphilis and yaws. The details of the development of the knowledge of the value of the major antisypilitic drugs (arsenicals, mercurials and bismuth compounds) and even fever^{49h} are fully covered in the monograph of León y Blanco^{49f} and in Holecob's⁴⁰ review to which the reader is referred for details. Mercury and the arsenicals were used as early as 1913 by Gratz³⁴ in Colombia. León y Blanco states, however, that the mercury salts were used empirically for more than a century for the treatment of this disease⁹ (1811). Although the modern arsenicals for pinta include mapharsen (arsenoxide) we find no reference to the application of massive arsenotherapy to this disease.

Epidemiology. Pinta is essentially a rural or suburban disease, occurring chiefly among individuals of poorer classes, laborers and persons living under unsanitary conditions. Its greatest distribution occurs in river valleys. In certain of the countries, there are distinct "pintogenous" zones. The disease is rare in the white persons. The majority of Cuban patients are negroes, while in Mexico, Venezuela, Colombia and Ecuador persons of the Indian race and mestizos are the most frequent sufferers.⁴⁸ Pardo-Castello and Ferrer⁶⁰ found the disease in white persons in 12 % of their Cuban cases. The disease occurs with equal frequency in males and females (51.52 % males and 48.48 % females in Mexican group^{18,49f}). It occurs mostly between the ages of 10 to 20 years. The primary lesion occurs especially on the extremities (in exposed parts). The possible mode of transmission is by direct contact, intimate and prolonged. The possibility of an intermediate host (insect vector) has been previously mentioned. Human and animal inoculation has also been dealt with above.

Clinical Manifestations. The extensive studies of León y Blanco in Mexico have led to an entirely new concept of the clinical course of

pinta. This new concept has been elaborated on by González Herrejón, Latapí and León y Blanco,⁴⁶ Gómez Farías, Briceño Rossi and Iriarte, Sáenz and his collaborators, Pardo-Castello and his associates, and Luis Blanco^{49,51} and in the paper of Pardo-Castello and Ferrer,⁶⁰ and Holcomb.⁴⁰ A summary of the important contributions to the knowledge of the clinical course of pinta may be found in the monograph of León y Blanco.⁴⁰ The historic considerations of the knowledge of the early lesions of pinta are reviewed by Pequeño.⁶² Excellent illustrations of Cuban cases are presented in the studies of Pardo-Castello and Ferrer and of Sáenz and his associates. Howard Fox's papers illustrate the Mexican and Colombian cases while Latapí and León y Blanco's⁴⁶ study profusely illustrates the early lesions of pinta.

The following is a condensed summary by León y Blanco of the course of pinta:

"Mal del pinto (pinta, carate) progresses through three distinct stages each showing different clinical, serological, and immunological characters.

"(a) The *primary stage* begins at the very moment of infection and lasts the period of time the lesion remains alone. Such period varies from individual to individual, being between 5 months and 1 year, or perhaps more. Clinically the primary or initial stage is characterized by the development of a papule at the point of infection, after an incubation time of 7 to 20 days. This papule gradually becomes an erythematous patch, variable in outline and size within 30 to 50 days. During its long-lasting evolution it spreads slowly around the affected area, or other papules begin to appear peripherally, which in turn increase, and with similar erythematous patches coalesce with the initial one.

"The appearance of these erythematous lesions varies greatly from one patient to another, as well as in the same individual, according to the developmental stage of the ill condition. The types more frequently observed are the trichophytoid, psoriasiform, lichenoid, and large patches of variable morphology.

"(b) The *secondary stage* is characterized by skin rashes or papules, which rapidly change with diversely outlined erythematous lesions and for more months have elapsed from the date of infection. This stage is reached after 5 to 12 or more months have elapsed from the date of infection. The initial lesion keeps on evolving during the secondary stage and becomes indistinguishable from the pinta.

"(c) *Tertiary or dyschromic stage* shows acromic or pigmentary spots, erythema, follicular keratosis, keratoderma and superficial atrophoderma. Cuban, Colombian, and American investigators have reported aortitis and pathological disturbances of the heart sounds; Mexican authors have also reported vagosympathetic disturbances as well as lymph node swellings generalized to the superficial nodules."

The dyschromic phases of pinta are well described by Fox⁵² as follows:

"Blue pinto consisted of slaty-blue pigmentation which was present in 25 cases on certain favorite sites, such as the face, waistline and trochanteric region and constituted the most unique feature of the disease. It appeared either as shiny aggregated puncta or as diffuse patches and in some cases was widely disseminated. On the head and neck, the bluish patches occurred in order of frequency on the nose and cheeks, the chin and lower part of the forehead, the neck, the lips, the ears and the vermilion border of the lips.

"White pinto, representing the terminal stage of complete depigmentation, was the most disfiguring and resembled ordinary vitiligo except that it was

always associated with other characteristic changes of the skin. It was present in 23 cases and showed a predilection for bony prominences such as the knuckles, elbows, knees and ankles. Another favorite site was the flexor surface of the wrist.

"Partial depigmentation was observed in 30 cases, occurring most frequently in association with other pigmentary changes. It was usually diffuse and often occupied extensive areas such as the greater part of the back and extremities. In some cases it consisted of pin head lesions intermingled with brownish hyperpigmented or bluish puncta, forming reticulated areas of most bizarre pattern. A favorite site for this type was the flexor aspect of the upper extremities, especially the forearms.

"Brownish hyperpigmentation was observed at the border of the vitiligid patches and as pea to bean sized cafe-au-lait spots on areas of partial depigmentation."

In addition to the cutaneous manifestations, pinta resembles syphilis in involving certain of the viscera, especially the heart and aorta. The cerebrospinal fluid changes have been cited above. Aortitis was reported by Thonnard-Neumann, Comacho Moya and Brewster⁷⁴ first; then by Pardo-Castello and by Sáenz and his collaborators. Pardo-Castello and Ferrer⁶⁰ found 20 cases (64.5% of 41 cases) with enlargement of the aorta and thickening of the aortic wall. The authors believed age was possibly a factor in some of the cases but high blood pressure was present in 8 cases, in 5 of which no aortic changes could be ascertained. Sáenz and his coworkers⁶⁸ observed cardiovascular lesions in 23.3% of their cases. They noted, incidentally, that keratosis of the palms and soles were frequent in the Cuban cases.^{49c}

Pinta thus represents another milestone in the efforts to evaluate the syphilis-like diseases. It is another example of the speed and the completeness with which modern investigative methods can organize from scattered beginnings the completely evaluated picture of a disease entity.^{7c} With the discovery of an organism, morphologically indistinguishable from *Spirochæta pallida*, the laws of Koeh have been fulfilled only a little less than in syphilis. But with this discovery of the treponemal cause of pinta, comes rationalization of effective therapy previously used empirically. With increased knowledge of the clinical aspects of the disease and the possible modes of its transmission, prophylaxis can be successfully employed. Credit is due to the indefatigable industry of the workers in our neighboring Latin American countries.

HERMAN BEERMAN, M.D.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

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ORIGINAL ARTICLES

THE PROBLEM OF PRIMARY SCIATIC NEURITIS

(AN ANALYSIS OF 55 CASES.)

By BERNARD J. ALPERS, M.D.

HERBERT S. GASKILL, M.D.

AND

BENJAMIN P. WEISS, M.D.

PHILADELPHIA, PA.

(From the Department of Neurology, Jefferson Medical College)

THE need for an analysis of a group of cases of sciatic neuritis may occasion some surprise. When, however, one reads that "from the reports in the literature it seems evident that there are very few cases of primary sciatic pain,"⁵ it becomes clear that it would be necessary to readjust one's ideas concerning sciatic neuritis if this statement were to be accepted at its face value. This concept, strange as it may appear to many, is supported further by the study of Grossman and Keschner,¹¹ who assert that "a primary mononeuritis or radiculitis of the sciatic nerve is extremely rare" and that practically all the cases of sciatica are secondary in origin. The tendency further to regard sciatic neuritis as a secondary manifestation of an osteoarthritis of the lumbar spine, with which it is assumed to be synonymous,⁶ makes a study of cases of sciatic neuritis or primary sciatica still more pertinent. Add to this the recent popularity of nucleus pulposus herniations as a cause of sciatica, and it becomes clear that the entire group of sciatica cases requires urgent analysis, particularly with reference to accurate means of differentiating cases of sciatic neuritis or primary sciatica from those of secondary sciatica.

If it is true that, as some believe, primary sciatica or sciatic neuritis is rare, it becomes necessary to analyze the cases which are regarded by neurologists as examples of this disease. Here one immediately encounters a paradox, for what is regarded by the neurologist as sciatic neuritis is believed by the orthopedist to be secondary to a distant irritative factor. With a larger view of the

many secondary causes of sciatica, some of which have been only recently revealed, it seems more consistent with the facts to state, not that sciatic neuritis is rare, but that secondary sciatica is much more common as a cause of sciatic pain, and that as compared with secondary causes, primary sciatica or sciatic neuritis is less common in the production of sciatic pain. This is somewhat different from the tendency to read sciatic neuritis out of the sciatica party. Because of these inconsistencies, we have reviewed our cases of sciatic neuritis in order to establish primarily the incidence of sciatic neuritis and to determine its recognition from other cases of sciatica.

Analysis of Material. All 55 cases, available for study, were carefully selected as authentic examples of sciatic neuritis. Cases of secondary sciatica were discarded. It was our desire to study the symptomatology as well as to indicate differences between the symptoms and course of primary and secondary sciatica.

Sex. The majority of our cases were found in males. Of 55 cases, 37 (67%) were males and 18 females. This coincides with the experience of others, but gives a somewhat higher incidence in males than do other series of sciatic neuritis.

Occupation. The incidence of sciatic neuritis in the more strenuous sex is borne out also by an analysis of the occupations of our 55 cases. It has been pointed out by many others that sciatic neuritis and sciatica are more prone to occur in persons who are exposed to changes in weather, or who are engaged in strenuous occupations. All but 4 of the males in our series were engaged in heavy work. Listed among the occupations were laborers, miners, street cleaners, shoemakers, machinist, engineer, roofer, cab driver, seaman, auto mechanic and so forth. In by far the greater number of cases the occupation involved exposure to changes in weather, and the use of brawn. In 4 cases there was nothing in the occupation of significance. Opposed to this array of brawny occupations stands the occurrence of sciatic neuritis in the women of our series, most of them occurring in housewives. Three cases developed in nurses.

Age. The age incidence varies from 16 to 72 years. The majority (41) of our cases occurred between the ages of 30 and 60 (73%).

TABLE 1.—AGE INCIDENCE OF 55 CASES OF SCIATIC NEURITIS

Age	No of cases
10-20 . . .	1
20-30	7
30-40	17
40-50	14
50-60	10
60-70	4
70-80	2

Sciatic neuritis therefore is a disease of middle and early old age, most of the cases occurring between 30 and 60 years of age, but it may develop before 30 and beyond 60 years.

Presenting Symptom. The presenting symptom in the majority of cases was pain referable to the hip or leg of one side. This pain often began in the hip and extended down the entire leg or only from the hip or back to the thigh. The presenting symptom was pain in the back.

Back Pain. Back pain is not a common symptom in sciatic neuritis. It was found in 17 of our 55 cases (about 30%). This is a low incidence if one were to take literally the assertion made by many authors that "sciatica" begins with an attack of lumbago which often persists late in the course of the illness. Its occurrence is of some value in differentiating between a primary sciatic neuritis and a secondary sciatica due to herniated nucleus pulposus, cauda equina tumor, structural deformity of the vertebræ, or one of the multifarious causes of the sciatic syndrome. While back pain occurs in one-third of the cases of sciatic neuritis it is more common in secondary sciatica.

Leg Pain. In 3 cases the pain was bilateral: all the others were unilateral. These cases however serve to emphasize the fact that bilateral sciatic pain may be due to a true neuritis, and need not necessarily indicate a tumor of the spinal cord. The old dictum that bilateral sciatic pain is always the result of structural causes needs revision, and this has come to be recognized by other investigators. Undoubtedly the majority of cases of bilateral sciatic pain are due to what may be termed structural causes such as tumor, arachnoiditis, or metastatic carcinoma, but the fact that pain in both legs may also be found in unqualified cases of sciatic neuritis needs to be more clearly recognized.

The *location* of the leg pain varies widely. It may be felt along the entire course of the sciatic nerve or in only portions of it.

TABLE 2.—DISTRIBUTION OF LEG PAIN IN 55 CASES OF SCIATIC NEURITIS

Location	No. of cases
Hip alone . .	0
Hip-thigh . .	10
Leg-ankle . .	15
Leg-toes or heel	14
Hip-knee . .	7
Thigh-calf . .	2
Knee-toes . .	2
Sacro-iliac . .	5

In the majority of the cases the pain extended from the thigh in the region of the hip to the ankle, toes or heel (29 cases). In some instances it extended from the hip to the thigh (10 cases), from the hip to the knee (7 cases), from the thigh to the calf (2 cases), or even from the knee to the toes (2 cases). In 5 cases the pain was in the sacro-iliac region without radiation.

The *duration* of the pain is of extreme interest. Sciatic neuritis is regarded as an acute disease, yet the incidence of prolonged pain is astoundingly high.

TABLE 3.—DURATION OF PAIN IN 55 CASES OF SCIATIC NEURITIS

Duration	No of cases
1 week	1
3- 4 weeks	10
5- 8 "	13
9-12 "	5
3- 6 months	9
7-10 "	2
10-12 "	2
1- 2 years	6
3- 5 "	7

Over half of the cases lasted from 1 to 12 weeks (29 cases), most of these lasting 3 to 8 weeks. Only 1 case lasted 1 week, the majority of the others persisting from 3 to 12 weeks. Nine cases lasted 3 to 6 months, and 13 cases from 1 to 5 years.

The cases lasting 3 to 12 weeks may be regarded as having a normal life history for sciatic neuritis, and as conforming to the generally accepted ideas concerning the duration of this illness. It is the instances of longer duration however which are of greatest interest, for it is when cases of sciatic neuritis stretch into periods of 6 months to 1 year or longer that doubt arises concerning the diagnosis. For this reason it is of paramount importance to know whether cases of sciatic neuritis may in fact last so long, and if so how they may be differentiated from cases of sciatic syndrome or secondary sciatica. A study of the cases which persisted for 1 year or more reveals the fact that in practically all these patients there were repeated attacks of sciatic neuritis. This group of cases represents therefore patients who have had recurrent attacks of sciatic neuritis lasting from 1 to 8 years. Of our 55 cases of sciatic neuritis, 13 (23%) may be regarded as recurrent. The duration of each episode of neuritis and the intervals during which the patient was free of pain could not be determined from the data at hand, the fact which seemed clearest being the tendency in these instances to recurrence of the attack of sciatic neuritis. The pattern of the attack as shown by the distribution of the pain and its nature varied often from one attack to another, but in some cases the distribution of the pain was the same with each repeated episode. These long cases of sciatic neuritis are of more than passing interest for they fall into a group in which, by virtue of duration of disease alone, the possibility of a secondary cause for the neuritis becomes pertinent. In most instances, when a case of sciatica which is assumed to be a sciatic neuritis lasts 2 to 5 years and is featured by recurrence of the sciatic pain, some secondary cause may be justifiably sought. The fact remains however that true sciatic neuritis may persist for long periods and that it need not be due to intraspinal or other causes. This is especially pertinent at the present time when, by virtue of advanced neurosurgical techniques, it is becoming a relatively common procedure to perform laminectomies on such cases. The point at issue is that mere longevity of symptoms is no indication of a

secondary cause of the sciatica unless other findings such as Roentgen-ray changes in the vertebræ and increased spinal fluid protein are present.

Little of clinical value is to be learned from the nature of the pain in the leg. It may be constant or intermittent. As a rule, for each particular attack it is constant, but it may be intermittent, with free intervals of pain for long periods or for very short periods. The pain is felt in the whole leg or in part of it and is not, as a rule, of a lancinating character. It is variously described as a dull ache or a sharp pain of various sorts, but little can be learned from the type of pain. Much more is to be learned from its distribution.

Movements of most sorts appear to increase the pain. It is almost invariably aggravated by walking, but frequently sitting, standing, or bending increases it. In some cases it is made worse by coughing, sneezing, or straining, all of which are frequently referred to as indicating evidence of a root lesion. In a few cases the pain is relieved by standing and aggravated by lying down. In general it seems clear that all movements which stretch the sciatic nerve, or which tend to stretch the muscles which are in spasm will produce an increase of the sciatic pain.

Paresthesias. Despite the fact that paresthesias are regarded as part of neuritis symptomatology, it is surprising to find how few of our cases complained of them. Only 7 of the 55 cases had paresthesias, variously referred to the back of the leg or thigh and sometimes in the foot.

Incontinence. In no case was there incontinence of the bladder or rectum, as was to be expected in cases of purely peripheral neuritis.

Nerve Tenderness. Nerve tenderness was found in 46 of 55 cases. The tenderness of the nerve was not always found along the entire length of the sciatic nerve. It was usually found everywhere along the sciatic trunk; in some cases only in the sciatic notch. Furthermore, muscle tenderness did not parallel nerve tenderness. The latter was almost always more pronounced than the tenderness of the muscles and was nowhere nearly as constant. It was a common experience to find nerve tenderness with little or no muscle tenderness. The stage of the sciatic neuritis must, of course, be considered in evaluating this feature, for it is quite possible that cases which had persisted for some time may have lost much of their muscle or nerve tenderness by the time they entered the hospital.

Lasègue's Sign. This, the sign of straight leg raising by which the sciatic nerve is stretched, was absent in only 7 of our cases. It is almost constant and is a sign of great importance, though it is by no means pathognomonic of sciatic neuritis. It is found as well in cases of sciatic syndrome due to many other causes.

In a few cases tenderness was found along the lumbar spinous processes, but the number of instances was not great enough to have any significance.

Reflex Changes. The Achilles reflex was decreased or absent on the side of the neuritis in 36 cases. In the other 19 cases it was

normal. The patellar reflex was never abnormal and no pathologic reflexes were found at any time.

Muscle weakness was found in none of our cases. It was surprising to find moreover that even in the long-standing recurrent cases no muscle atrophy was visible. In none of our cases was the muscle weakness ever of a greater degree than could be accounted for by protection against leg pain. This held true even in cases of long duration and it may be a point of value in differentiating cases of sciatic neuritis from those of secondary sciatica. While muscle weakness is by no means constant in the latter, its mere occurrence would tend to favor secondary sciatica, judged by its absence in our group of cases of sciatic neuritis.

Sensory Changes. These also were strikingly absent in almost all the cases except for a few with slightly decreased pain sensations over the lateral aspect of the thigh or leg. Sensory changes like muscle weakness and wasting were strikingly absent in the great majority of cases no matter what the duration of the disease.

Analysis of Causes. The analysis of causes of our cases of sciatic neuritis is, of course, difficult. Preëminent among the causes which stand out are those related to foci of infection. Diseased tonsils were found in 28 cases. This does not mean, of course, that tonsillar disease was responsible for the sciatic neuritis in all these instances. In only 8 cases could it be demonstrated that removal of the tonsils resulted in relief and cure of the neuritis. In 20 cases carious teeth were found, but in only 6 instances was pain relieved after their removal. Acute or chronic sinus disease was found in 12 cases; prostatitis was present in 8 cases.

The relation of these foci of infection to the neuritis is difficult to evaluate. It is impossible to say absolutely that the removal of the infected foci resulted in the cure of the sciatic neuritis. Yet the conclusion is inescapable that in the cases relieved by removal of tonsils or teeth the recovery was quick in most cases following their removal and in some instances dramatic.

The incidence of other factors was not as high as that of foci of infection. In 17 cases osteoarthritis of the sacro-iliac joints or of the lumbar vertebræ was found. Whether the arthritis was sufficient to cause the sciatic pain is at least open to discussion. In only 2 cases was sacralization noted, and in only 2 was osteoarthritis of the hip discovered.

Diagnosis. The diagnosis of sciatic neuritis and its differentiation from secondary sciatica is not difficult. The cases of sciatic neuritis are characterized invariably by tenderness of the nerve trunks and usually also by tenderness of the muscles of the thigh and calf. Nerve trunk tenderness particularly in the sciatic notch and popliteal spaces was present in some degree in every case in our series; muscle tenderness was found in only 8 instances. The degree of nerve tenderness varies greatly, in some cases being pronounced, the others less severe; but it is always present. Severe nerve tenderness was found in 22 cases, moderate in 24, and mild nerve tenderness in

9 cases. No such tenderness is found along the nerve trunks in secondary sciatic in the majority of cases. It is well known that compression of the sciatic nerve or of any peripheral nerve at a single point may produce tenderness along the nerve trunk at a distance from the point of compression. This is unusual, though it serves to prove that nerve trunk tenderness cannot be invariably interpreted as indicating a primary neuritis. The percentage incidence of such tenderness in cases of secondary sciatica has not been determined in view of its many causes, but its occasional incidence in the secondary form, as compared with its invariable occurrence in primary sciatica, serves but to demonstrate that nerve and muscle tenderness are typical features of the one and an exceptional characteristic of the other:

All other diagnostic criteria of sciatic nerve involvement—weakness or atrophy of the leg muscles, decrease or absence of the Achilles reflex, pain on stretching the sciatic nerve, sensory disturbances and so forth—are as characteristic of one form of sciatica as the other and cannot be used in the differentiation of sciatic neuritis from secondary sciatica. Special signs such as the Lasègue's, Neri's and others, all of which depend on the stretching of the sciatic nerve, are also characteristic of both groups, as would be expected. Laboratory studies are of relatively little value except that evidence of structural disturbances in the vertebræ, pelvis, spinal canal, or muscles indicates a secondary rather than a primary sciatica. Spinal fluid abnormalities such as xanthochromia and increased protein content are characteristic of spinal cord tumor or herniated nucleus pulposus, but increased protein in the spinal fluid may be found in the special forms of neuritis such as the Guillain-Barré syndrome.

In the last analysis the diagnosis of sciatic neuritis as distinct from that of secondary sciatica depends upon the presence of tenderness over the sciatic nerve with or without tenderness of the thigh and leg muscles. In all other physical respects, exclusive of laboratory findings, cases of sciatic neuritis and secondary sciatica are similar.

Discussion. The problem of sciatica is so greatly confused that a review of the more pertinent points under discussion appears to be desirable. Not only is there wide disagreement concerning the cause of the various forms of sciatica, but there is as great divergence concerning their treatment.

Classification. There seems to be general agreement that not all sciaticas can be thrown into a single grouping. This at least is a step in the right direction, for it emphasizes immediately the multiplicity of causes of the sciatic syndrome. Many groupings have been suggested, the simplest and probably most satisfactory being that of Feiling,⁹ who divided the sciaticas into: 1, primary or essential sciatica; and 2, secondary or symptomatic sciatica. The cases of secondary sciatica are clear enough; they include all the cases of sciatic pain which can be shown to be secondary to a specific struc-

tural cause of some sort. In the primary group however Feiling includes not only cases of sciatic neuritis which are regarded as cases of true neuritis, but also a large group of cases which he calls sciatic neuralgia, the cause of which is unknown or cannot be determined. These cases have been referred to by others as idiopathic sciatica. The inference that a primary sciatica is an idiopathic sciatica is reflected further by the views of Douthwaite,⁷ who divides the sciaticas into primary and secondary, further subdividing the primary group into those of peripheral and those of central origin. He states moreover that no subgroup may be termed primary in the presence of a clearly determinate or specific cause. Here the inference is clear that primary sciatica is sciatica of undetermined origin, the vast majority of which in the opinion of Douthwaite are cases of sciatic neuritis. Chavany⁸ divides the sciaticas into true, symptomatic sciatica and pseudosciatica. The further subdivision of the sciaticas into high, middle and low types (Sicard²⁴) has some clinical usefulness. Harris¹² refers only to high and low types. High sciaticas are due to lesions of the roots or lumbosacral plexus. Middle sciaticas are the result of lesions of the plexus or of the nerve trunks from the sacrosciatic notch to their entry into the thigh. Low sciaticas are due to involvement of the nerve in the popliteal space.

A classification into primary and secondary sciatica serves all practical purposes, is accurate and at the same time emphasizes the fact that sciatica is variously produced by many causes. The inference that all or some of the primary sciaticas are idiopathic in origin needs further study and will be dealt with under a discussion of the causes of this syndrome.

Causes of Sciatica. There are many causes of sciatica. No useful purpose can be served by an enumeration here of the many conditions which may give rise to the syndrome. It is important however to emphasize the multiplicity of causes of sciatica in order to prevent uniformity in the treatment of a condition which is variously produced.

In the evaluation of the sciatic problem it becomes clear that the cases of sciatic neuritis must be considered quite apart from those of other origin. The fact that no cause can be established for such cases should occasion no greater surprise than for other cases of neuritis, and certainly does not justify their classification as idiopathic. To say that most cases of sciatica are secondary to diseases of the pelvis, vertebrae, or other organs, is not to deny the existence of sciatic neuritis. Evans,⁸ for example, reports 40 cases of what he terms primary or idiopathic sciatica. In many cases of sciatic neuritis the precise cause is not disclosed, yet the neuritis cannot be denied. The exquisite muscle and nerve tenderness seen in these cases stamps them as instances of primary neuritis frequently of undetermined origin. In Feiling's clear discussion of the sciatica problem, sciatic neuritis is regarded as a true neuritis the causes of which are uncertain. He discards foci of infection as a vital cause

and says, "I doubt if I can recall a single example out of the many cases of sciatica I have seen when the finding of a septic focus, followed by its appropriate treatment, seems to have affected to any appreciable extent the course of the disease." Our cases do not bear out this belief. In some of them the removal of infected teeth or tonsils appears to have improved the sciatic neuritis greatly, but in many others no such causal relationship could be established. Despite this failure to establish a precise cause in many of the cases of sciatic neuritis, they must nevertheless be regarded as true or primary neuritis, with all the features of a neuritis elsewhere in the body. Careful inquiry into bacteriotoxic, metabolic chemical, virus, or nutritional causes may reveal no definite cause for the neuritis, but the same is true of other forms of neuritis as well. Despite all efforts to establish it, there is often no indication of the exact cause of a neuritis involving other parts of the body. For many cases, such a cause can be determined, but for many others it is not clear. Yet no recourse is taken to the term idiopathic neuritis and there seems no real justification for the term in relation to sciatic neuritis. In some instances, as Lichtman¹⁶ has pointed out, sciatic neuritis may be the precursor of hepatic insufficiency, and may be an early manifestation of a disease process which may lead to hepatic disease and hepatic insufficiency.

It is precisely this ignorance of the origin of sciatic neuritis which has led many to assume that such cases are few in number and that those which do exist are often of a secondary type. Hence the inference by Danforth and Wilson,⁶ that what is regarded by neurologists as sciatic neuritis is in reality secondary to disease of the lower lumbar spine or sacro-iliac joints, the neuritis being regarded as a secondary manifestation. Hence also the increasing emphasis on the secondary causes of sciatica, all of which represents, of course, a healthy outlook, but adds nothing to our knowledge of primary sciatic neuritis. It tends rather to tip the balance in favor of looking for secondary causes when they are not present, even to the performance of operative procedures. Thus, Williams²⁸ reports changes in the bones of joints in 94% of 107 cases of sciatica. MacKinnon²⁰ asserts that all the features of idiopathic sciatica are due to an infectious lumbosacral arthritis. Involvement of the fifth lumbar root in its foramen by infection or arthritis is regarded by Danforth and Wilson,⁶ Cochrane,⁴ Furnrohr¹⁰ and Putti²³ as an important cause of sciatica. Buckley² found a predominance of affections of the lumbar and sacral articulations as causes of sciatic pain among 108 cases of sciatica. More recently attention has been directed to herniation of the nucleus pulposus in cases of sciatica.^{18,19,25,26}

In spite of the frequent affirmation that sciatica is the result of many causes, there seems to be a persisting tendency to explain different sciatic syndromes by the same cause. For this reason one finds that sciatic neuritis is either denied a place of its own or is regarded as due to some secondary cause such as osteoarthritis of

the spine. It is this fallacy which must be averted in a consideration of sciatica cases.

Pathogenesis of Sciatic Pain. The origin of the sciatic pain varies, of course with its cause; but here too the assumption is frequently made that most if not all cases of sciatica can be explained by a single pathogenetic mechanism. Some believe that sciatica is related to various forms of neuritic disease.²⁷ That it is in some instances a true neuritis cannot be denied, though plausible explanation may be found to the nerve tenderness and pain. Harris believes that the neuritis in such cases is a perineuritis of the sciatic sheath in the region of the sciatic notch where the nerve escapes from the pelvis into the buttock.

The concept of a neuritis satisfies relatively few cases however, and obviously can apply only to the small group of primary sciaticas. Hence, other explanations for the sciatic pain have been sought. It is clear that no difficulty is offered by cases of sciatic pain with an obvious structural deformity such as a spinal cord tumor, herniated nucleus pulposus with compression of the lumbosacral roots, pelvic tumor with compression of the lumbosacral plexus, Pott's disease, or other lesions too numerous to mention, with obvious reasons for the sciatic pain. The difficulty lies in explaining the cause of the pain in many cases which have been erroneously regarded as neuritis or have been carelessly regarded as the result of sacro-iliac strain or arthritis or lumbar arthritis, when no evidence for such a background has been demonstrable. For such cases Danforth and Wilson after a careful study of cadavers have offered the explanation that the sciatic pain is due to an inflammatory process of arthritic or traumatic origin causing irritation of the fourth and fifth lumbar roots. Their studies revealed that the intervertebral foramina of the lumbar roots vary in size and that the largest lumbar root, the fifth, is enclosed in the smallest canal and therefore easily susceptible to compression by encroachment. Their clinical studies support their ideas, but it may be objected that the pain of sciatica is frequently outside the nerve distribution of the fifth lumbar root and that it is frequently not a root pain. The concept has received wide support especially from orthopedists.^{13,28}

That this idea does not satisfy all the conditions found in all the cases of this group is shown by the contention of Ober,²² who maintains that many cases of so-called sacro-iliac strain with low back pain and sometimes with sciatic pain are the result of a tight ilio-tibial band. Severe sciatica, according to Ober, is often associated with the condition. A concept somewhat allied to this is that of Nutter,²¹ who believes that sciatica is sometimes due to unusual fascial bands or fascial thickening around the sciatic nerve in the neighborhoods of the sciatic notch. He points out two areas of thickening of the fascia: 1, at the upper border of the piriformis where this muscle is contiguous with the lower edges of the gluteus medius and minimus, and, 2, at the lower border of the piriformis immediately lateral to the great sciatic nerve. Nutter²¹ believes that

when the intervals between the muscles are greater than normal, fascial bands may focus. Of 10 cases, 4 were cured by exploration, but none of these showed evidence of fascial bands.

The conception of Bruce,¹ that sciatica is due to an affection of the hip joint, has found little support, though Bruce found 48% of 676 cases of sciatica with evidence of rheumatism or gout. His theory is based on his observations that wasting of the hip muscles is very decided in nearly all cases of sciatica, and on the further observation that there is tenderness on pressure over the capsule of the hip joint. Similarly, an attempt to explain the obscure cases of sciatica by invoking sacro-iliac disease has not succeeded in the absence of evidence of such disease, though Hertzler¹⁴ claims that sciatica is due to a synovitis of the sacro-iliac joint and that the sciatica is due to an irritation of the nerve by the joint inflammation.

A purely muscular origin of the pain in sciatica is offered by Helweg,¹³ who found in the majority of 750 cases changes in the muscles of the gluteal region and the back of the leg. All these cases showed nerve tenderness and positive leg-raising signs; whereas cases with pain in the leg without these signs failed to show the muscle changes which Helweg emphasized. He therefore placed in a special group the cases with pain in the leg, muscle changes, and positive leg-raising and nerve tenderness signs. He regarded the firmer consistency of the muscles of the gluteal and thigh regions in these cases as due to a myopathy, characterized by an increased firmness of the muscles to palpation. This myopathy he regards as the result of an "intense and long-continued use of just those muscles or parts of muscles which the palpation examination show to be the seat of the myopathy." Helweg believes that in cases which develop sciatica and therefore myopathy, unusual demands are made on the muscles in question. Even in cases of sciatica due to bone disease he maintains that the muscle disturbance is the primary cause of the pain. The disturbance in the Achilles reflex is due to the accumulation of fatigue substances. Janssen¹⁵ objects that the theory does not explain the tenderness of the nerve trunk, and that the muscles have never been examined directly.

Opposed to this view is that of Lindstedt,¹⁷ that sciatica in the majority of cases is a pure neuralgia without anatomic findings in the nerve, and that it arises from irritating conditions in the periphery of the nerve which cause pain radiating into the whole of the sciatic area.

Summary. The concept that primary sciatic neuritis is rare is not supported by the evidence. We report 55 such hospitalized cases, all of which were severe. It is quite probable that many more cases of sciatic neuritis are seen in general practice, which recover without hospitalization. It is important that this fact be borne in mind in view of the present-day tendency to regard most cases of sciatic pain as being of secondary origin. While cases of secondary sciatica very probably outnumber the primary cases, our experience leads us to the conclusion that true sciatic neuritis is not a rarity. There

appears to be no justification moreover for the concept of an idiopathic sciatica any more than for other forms of neuritis. The causes of sciatic neuritis are those of neuritis in general and those cases for which no cause is found should not be regarded as idiopathic.

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A NEW TEST OF LIVER FUNCTION—THE TYROSINE TOLERANCE TEST

By F. W. BERNHART, Ph.D.

HEAD OF SECTION OF BIOCHEMISTRY, RESEARCH DIVISION

AND

R. W. SCHNEIDER, M.D.

STAFF MEMBER, ASSISTANT IN MEDICINE, CLEVELAND CLINIC
CLEVELAND, OHIO

ABNORMALITIES in the metabolism of tyrosine in the presence of liver disease have long been recognized, but of the many liver function tests employed clinically none has been designed to test the ability of the liver to metabolize this important amino acid. This lack is principally due to the fact that, up to the present time, no reliable quantitative method for the determination of blood tyrosine has been described. The purposes of the present communication are chiefly to describe a quantitative method of blood tyrosine determination, to present a curve of tyrosine tolerance in normal

subjects, and to demonstrate changes occurring in certain types of liver disease. Correlation of its sensitivity, as compared to other tests of liver function, has been made whenever possible.

Impairment in amino acid metabolism in hepatic disease was probably suggested first by Frerichs,¹ who noted the presence of tyrosine and leucine crystals in the urine in cases of acute yellow atrophy. Lichtman,⁵ using a quantitative analysis for tyrosine in urine, further observed an increased tyrosinuria in various types of liver disease. Jankelson,^{3,4} who employed a qualitative method of tyrosine analysis, was unable to demonstrate the presence of tyrosine in normal blood but found various levels of tyrosinemia in a high percentage of patients with liver disease.

These observations of tyrosine metabolism suggest that a tyrosine tolerance test may be of value in the diagnosis of liver disease.

Methods. *Determination of Blood Tyrosyl.* A modification of the Millon reaction, using the photoelectric colorimeter, was found suitable for blood tyrosyl. The Millon reaction is not specific for tyrosine but is specific for the characteristic phenol group of tyrosine. The term "tyrosyl" refers to the tyrosine and closely related metabolic products which give the test. Spectrophotometric analysis shows that the color produced in blood filtrates is the same as the color produced in pure tyrosine solutions, indicating that metabolic changes in the side chain of tyrosine have little, if any, effect upon the color produced by the reaction. A photoelectric colorimeter is necessary because the color produced by the normal concentration of blood tyrosyl is not intense enough to be easily compared in the visual colorimeter. The Klett-Summerson photoelectric colorimeter was found satisfactory.

Six cc. of blood was drawn and added to dry oxalate (0.15 mg. per cc. of blood). The required amount of filtrate was obtained from 5 cc. of blood. A 1 to 5 blood filtrate was prepared by adding 2 volumes of water, 1 volume of 10% sodium tungstate and 1 volume 1N H_2SO_4 to 1 volume of the oxalated blood, then shaking vigorously and centrifuging. To 7 cc. of the clear centrifugate contained in a centrifuge tube were added 0.5 cc. 7N H_2SO_4 , 1.5 cc. 15% HgSO_4 in 6N H_2SO_4 and 1 cc. of 0.1N H_2SO_4 .^{*} To the standard containing 7 cc. of the same filtrate, 0.5 cc. 7N H_2SO_4 and 1.5 cc. of the mercury reagent were added 1 cc. of tyrosine solution (0.05 mg. in 1 cc. of 0.1N H_2SO_4). The tubes were heated 8 minutes in a boiling water bath, then cooled below room temperature in running water. After adjusting the volume to 10 cc. with water the tubes were centrifugalized and 8 cc. of the clear liquid placed in the colorimeter cell. The blank reading was determined, 0.05 cc. of 5% sodium nitrite solution added, and the mixture shaken. The color produced was read after 4 minutes, using a filter with maximum transmission at 500 m μ . Up to 0.6 mg. of tyrosine added to each cubic centimeter of blood was quantitatively recovered by this method. Duplicate determinations agreed within 3%.

The standard tyrosine solution did not deteriorate for at least 6 months when kept refrigerated.

Calculations. The following calculations are for the Klett-Summerson colorimeter. With other instruments the calculation, although the same in principle, will vary in detail. Three readings were taken: (1) Blank reading of unknown. This reading may be assumed to be the same for the known. (2) Unknown reading. (3) Known reading.

The blank reading (1) is subtracted from (2) and (3), giving the true color value in the 2 tubes.

* For detailed directions for the preparation of the reagents see Folin, O., and Marenzi, A. D.: J. Biol. Chem., 83, 89, 1929.

True known reading—true unknown reading = k , the color produced by
 (3-1) (2-1)
 the known added amount of tyrosine.

$$\frac{\text{True unknown reading}}{K} \times \frac{100}{1.4} \times 0.05 = \text{mg. tyrosine equivalent in 100 cc. of blood.}$$

Tyrosine Tolerance Test. Four grams of tyrosine,* 5 gm. of casein and 4 to 5 drops of 1% phenolphthalein solution were placed in 250 cc. of water in a 1 liter Erlenmeyer flask. While the flask was heating over a Bunsen burner, 5N NaOH was added drop by drop and the flask shaken until the tyrosine and casein were in solution and the phenolphthalein color persisted. An excess of NaOH should be avoided. The addition of casein increases the solubility of the tyrosine.

Two drops of oil of peppermint added to the mixture help to disguise the alkaline taste. The flavored solution was well tolerated, even by extremely sick individuals.

The tests were made after an overnight fast, water being allowed until midnight. After withdrawal of a sample of blood the tyrosine solution was administered orally. Blood samples were taken 1, 2 and 3 hours after ingestion of the tyrosine solution.

Other Liver Function Tests. (a) *The sodium benzoate conversion test* described by Quick⁶ was made by administering 6 gm. of sodium benzoate. Excretion in the urine of less than 3 gm. of hippuric acid in 4 hours is regarded as evidence of hepatic dysfunction.

(b) *The Takata-Ara test* was made and interpreted according to the directions of Heath.²

(c) *Prothrombin Time.* The Quick method⁷ was used, and the clotting time obtained was compared with the clotting time of a sample of normal blood which was treated in the same manner.

(d) *The bromsulfalein excretion test* was made by injecting 5 mg. of the dye per kilo of body weight. When this dosage is used the normal retention after $\frac{1}{2}$ hour is considered to be from 0 to 10%.

(e) *The galactose tolerance test* was made by administering 40 gm. of galactose. Excretion in the urine during a 4-hour period of over 3 gm. of galactose is regarded as evidence of hepatic dysfunction.

Results. Normal Fasting Level. The concentration of tyrosyl in the normal fasting subject is equivalent to 1 to 1.8 mg. of tyrosine per 100 cc. of blood. This result is in contrast with the observations of Jankelson^{3,4} who found no tyrosyl value in the blood of normal fasting individuals, and this difference in results serves to emphasize the increased sensitivity of the present quantitative method.

Tyrosine Tolerance in Normal Subjects. Administration of 4 gm. of tyrosine to 10 presumably normal subjects yielded the data shown in Table 1.

TABLE 1.—TYROSINE TOLERANCE IN NORMAL SUBJECTS

Sample (hrs. after ingestion of tyrosine)	Blood tyrosyl concentration (mg./100 cc.)		
	Minimum	Maximum	Average
Fasting	1 0	1 8	1 4
1 hr.	4 0	6 4	5 4
2 hrs.	3 6	5 0	4 6
3 hrs.	2 9	4 0	3 4

* Obtained from the S. M. A. Corporation, Chagrin Falls, Ohio

Tyrosine Tolerance in Liver Disease. After a curve of tolerance to ingested tyrosine in normal subjects was obtained, an attempt was made to apply the test clinically to patients with obvious liver disease and others with suspected liver disease. In some instances of severe hepatic insufficiency, especially advanced cirrhosis, the fasting blood tyrosyl level was significantly elevated beyond the upper normal limit of 1.8 mg. per 100 cc. of whole blood. In 1 instance a fasting level of 4.9 mg. was obtained. In every instance of cirrhosis of the liver thus far studied, the tolerance to orally ingested tyrosine was diminished. In some patients levels as high as 15 mg. were found 1 hour after consumption; furthermore, the hypertyrosinemia persisted at levels as high as 8 to 11 mg. for as long as 3½ hours after ingestion of the substance. This indicates not only an impairment in the ability of the liver to metabolize ingested tyrosine, but shows that the resulting tyrosinemia persists for long periods of time and often remains a permanent part of the abnormal body chemistry comparable to the hyperglycemia of untreated diabetes mellitus.

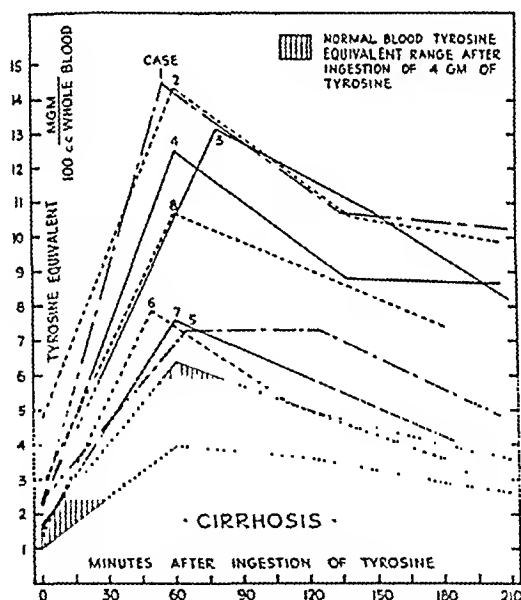


FIG. 1.—Tyrosine tolerance curves in cases of cirrhosis of the liver.

Case Reports. **CASE 1.** A white woman, aged 44, examined on November 19, 1941, complained of swelling of the abdomen of 5 months' duration. She had been almost constantly inebriated for 3 years following the death of her husband. In July, 1941, she noted onset of mild icterus and gradually increasing ascites. Repeated paracenteses were performed before admission. Anorexia, weakness and chronic dyspepsia had been noted.

Physical examination revealed a pallid, sickly-looking woman with a sallow skin. The abdomen was markedly protuberant; a fluid wave and shifting dullness were present. Six thousand cc. of straw-colored fluid was removed by abdominal paracentesis.

Her blood count revealed 4,090,000 red blood cells per c.mm., 55% hemoglobin per 100 cc. (8.5 gm. by Haden-Hauser) and a volume index of 1.14. Total blood proteins were 5.2%. A bromsulfalein test of liver func-

tion revealed 44% retention of dye in 30 minutes. A Takata-Ara test on ascitic fluid revealed a positive reaction.

A tyrosine tolerance test revealed marked impairment in function (Fig. 1).

CASE 2. A white man, aged 55, first examined on November 15, 1941, complained of vomiting of blood, diarrhea, a loss of 20 pounds in weight, and abdominal swelling. He had been consuming large quantities of alcohol for 8 years. Two months before admission he experienced painless hematemesis and melena. For 4 weeks he had noted swelling of the abdomen. Hematemesis and melena had recurred repeatedly and he was admitted in a semi-stuporous condition.

Physical examination revealed slight icterus of the skin and conjunctivae. The abdomen was tense with shifting dullness and a palpable fluid wave.

The blood count on admission was 2,400,000 red blood cells per c.mm. with 29% of hemoglobin (4.5 gm. Haden-Hauser) per 100 cc. The blood Takata-Ara test was positive. Total blood proteins measured 5.7%.

The prothrombin time was 34 seconds, as compared to a normal of 16 seconds. The patient improved following three blood transfusions and symptomatic care. The tyrosine tolerance curves obtained is shown in Figure 1.

In the same figure are shown 6 other cases of advanced cirrhosis of the liver. In 6 of these 8 cases, a history of excessive use of alcohol was obtained. In 1 case (Case 7) dinitrophenol had been taken to reduce weight 8 years previously. Hepatomegaly was present in all cases, ascites in 5 and jaundice in 3. The Takata-Ara test was positive in 2 of 3 cases tested. The prothrombin time was delayed in the 4 cases tested, and the oral hippuric acid test was negative in the 1 case receiving this test (Case 3). One individual (Case 5) died 2 days after the test was given. Delayed absorption of the ingested tyrosine seems possible since the character of the response in this instance differed from all the others. This patient presented intense jaundice with an icterus index of 120.

Table 2 compares the results obtained with the tyrosine tolerance test and the percentage of bromsulfalein retention after $\frac{1}{2}$ hour. The icterus indices are included in each case.

TABLE 2.—COMPARISON OF THE PERCENTAGE OF BROMSULFALIN RETENTION AT THE END OF 30 MINUTES WITH THE PERCENTAGE INCREASE OF BLOOD TYROSINE ABOVE THE MAXIMUM NORMAL VALUES AFTER INGESTION

Cases	Icterus index	Bromsulfalein retention	% blood tyrosine increase over normal maximum value			
			Fasting	1 hour	2 hours	3 hours
1	17	41	30	120	130	160
2	16	Not done	30	100	90	120
3	50	40	30	70	140	110
4	30	18	170	120	130	160
5	120	80	30	10	50	40
6	4	14	-20	20	0	-10
7	4	20	-10	20	20	0
8	6	40	40	70	50	90

Non-cirrhotic Hepatic Disease. The tyrosine tolerance curves obtained in 8 patients with a variety of other abnormalities of the liver or biliary tract but without clinical evidence of cirrhosis are shown in Figure 2.

The first patient (Case 9) had diabetes and a rather marked deficiency state, chiefly in the vitamin B complex. A bromsulfalein test revealed 14% retention of dye. The second patient (Case 10) also had deficiency disease and in addition had rather marked rheumatoid arthritis. A bromsulfalein test in this individual revealed 20% impairment of function. Patients indicated in Curves 11, 13 and 14 had chronic cholecystitis and stones. Two of the

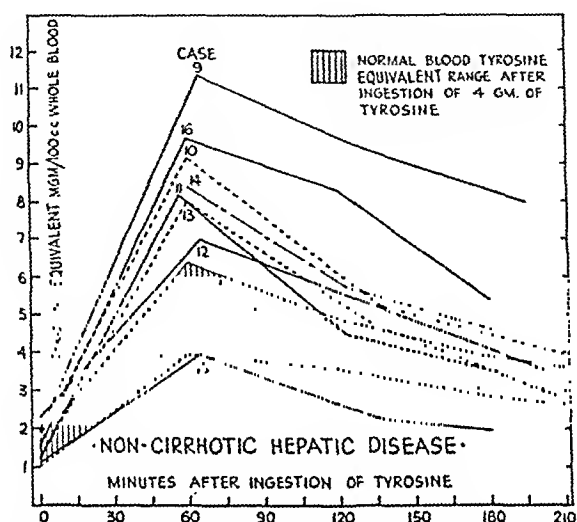


FIG. 2.—Tyrosine tolerance curves in cases of non-cirrhotic hepatic disease.

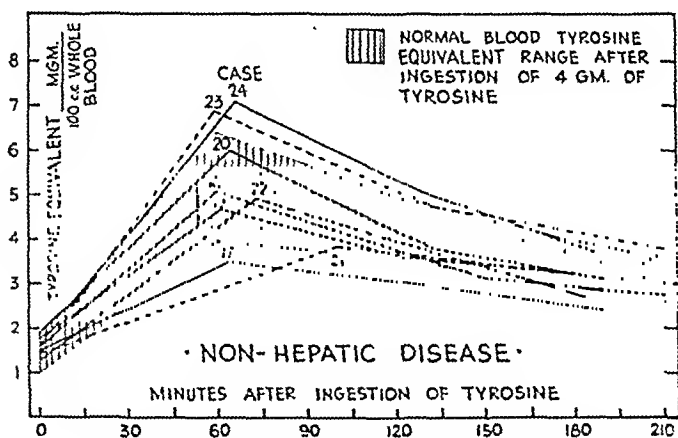


FIG. 3.—Tyrosine tolerance curves in cases of non-hepatic disease.

3 tested had normal values by the oral hippuric acid test. One patient (Case 12), at operation, had a carcinoma of the common bile duct and a normal preoperative galactose tolerance test. Case 15 had acute cholecystitis and normal hippuric acid tests on 2 occasions. At operation, the liver appeared normal. The remaining patient (Case 16) had hepatocellular jaundice with icterus index of 80. The galactose tolerance was within normal limits, and the hippuric acid test revealed 58% of normal function.

Non-hepatic Disease. Studies were conducted in a group of patients with a variety of clinical conditions, special emphasis being placed on individuals in whom there was no history nor clinical evidence of liver disease. Three patients (Cases 19, 20 and 24) had chronic gout. One individual (Case 17) had periarthritis and a past history of catarrhal cholangitis. One patient (Case 21) had intermittent claudication and the remaining 2 (Cases 18 and 23) had simple obesity and mild diabetes. There was no evidence of impaired tyrosine tolerance in 6 of the 8 cases studied. The results obtained in Cases 23 and 24 suggest that slight elevations over the normal range of tyrosine tolerance often may occur in non-hepatic disease.

Summary and Conclusions. 1. A reliable method for the quantitative determination of blood tyrosyl had been described, and a normal curve of tyrosine tolerance has been presented, as based on the results obtained in 10 normal subjects.

2. Eight patients with advanced cirrhosis revealed abnormal curves. Other patients with less well-defined liver disease also demonstrated abnormal tyrosine tolerance curves.

3. The results obtained from the test thus far indicate that it is more sensitive than the bromsulfalein and other common tests of liver function. It appears to be reliable, economical, safe and well tolerated. Its sensitivity, as compared to other liver function tests, needs further study, and a final opinion in this regard cannot be made at present. The results show definitely that severe liver disease interferes with the metabolism of tyrosine.

4. Besides yielding information on tyrosine tolerance in liver disease, the present results suggest that valuable information may be obtained by the determination of the fasting blood tyrosyl level in patients with suspected liver disease. Perhaps a simplified test in which only the fasting value and the blood tyrosyl concentration 1 hour after ingestion of tyrosine are determined would give sufficient information from which to draw valuable conclusions concerning functional impairment of the liver.

5. Tyrosine and closely related metabolic products are normal constituents of blood. Their concentrations in the fasting state are equivalent to 1 to 1.8 mg. of tyrosine per 100 cc. of blood.

6. Ingestion of tyrosine by normal subjects causes a prompt rise in blood tyrosyl, which reaches a maximum at the end of about 1 hour; following this there is a gradual fall toward the fasting level.

7. Blood tyrosyl levels may be elevated in the fasting state in patients with certain liver diseases, particularly cirrhosis.

8. The ingestion of tyrosine by patients with cirrhosis of the liver frequently results in markedly elevated blood tyrosyl levels.

9. The present results suggest that the tolerance to tyrosine may prove valuable as a test of the metabolism of tyrosine by the liver and thus serve as a valuable test of liver function.

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FAMILIAL MEDITERRANEAN TARGET-OVAL CELL SYNDROMES

BY WILLIAM DAMESHEK, M.D.*

PROFESSOR OF CLINICAL MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL
BOSTON, MASS.

(From the Joseph H. Pratt Diagnostic Hospital and the Blood Clinic and Laboratory
of the Boston Dispensary)

TARGET cells are unusually thin erythrocytes which have the appearance of "bull's eyes" or targets in stained blood films, and are unusually resistant to hypotonic solutions of sodium chloride. In 1940, under the designation of "target cell" anemia, I⁴ reported the case of a young man of Italian origin who presented a moderately severe hypochromic anemia with numerous target cells, marked splenomegaly, moderate hemolytic icterus and the generalized osteoporotic changes commonly seen in Cooley's erythroblastic anemia. Since no nucleated red cells were present in the peripheral blood, it was believed that the case probably represented an "anerythroblastic" and relatively mild variant of Cooley's erythroblastic anemia. In the latter rather rare condition, which occurs in children of Mediterranean origin (Italian, Greek and Syrian), one of the outstanding features is the presence of numerous nucleated red cells. Marked hypochromic anemia, splenomegaly, generalized bone changes, increased hypotonic resistance of the red cells, and the evidences of increased hemolysis are concomitant features. Death almost invariably occurs before the age of 12, therapy with iron, liver extract and splenectomy being ineffective.¹

Since but few cases of Cooley's anemia survive to adolescence or the adult state, the mechanism of inheritance has been obscure. A few years ago, Caminopetros² found that certain siblings of cases of Cooley's anemia had increased hypotonic resistance of the red cells and suggested that this abnormality might be inherited in a Mendelian recessive fashion. Our studies on this point have revealed mild target cell syndromes in *both* parents and in certain siblings of cases of Cooley's anemia—findings which indicate that Cooley's anemia is definitely inherited, although the exact mode of inheritance remains to be worked out.

* Aided by grants from the Charlton Fund, Tufts College Medical School.

In the paper referred to above,⁴ the suggestion was advanced that the fundamental fault in Cooley's anemia might center about the target cell, which indeed might be the inherited defective factor. Further studies, chiefly in Italians have demonstrated that various syndromes presenting among other features target cells and increased hypotonic resistance of the erythrocytes are not uncommon and are usually familial and hereditary. It has been possible to arrange these cases in groups ranging in severity from Cooley's erythroblastic anemia and the previously reported case of target cell anemia to very mild cases of hypochromic anemia with target cells, elliptical and oval cells, and basophilic stippling.

Several of these syndromes (including Cooley's anemia) have already been reported as separate diseases under different headings. These include the following: Familial Hematopoietic Disorder in Italian Adolescents and Adults, Resembling Mediterranean Disease (Thalassanemia) (Wintrobe *et al.*⁹); Familial Microcytic Anemia (Strauss, Daland and Fox⁸); Microcytic, Hypochromic Anemia Associated With Splenomegaly and Refractory to Treatment (Eliel and Bayles⁵); *La Syndrome di Cooley (Anemia Mediterranea) Nell' Adulto* (Chini³); *Anemia ipochromica splenomegalia emolitica con ovalocitosi (Ellitocitosi), poichilocitosi ed aumento della resistenza osmotica dei globuli rosse* (Introzzi⁶). The possible relationships between these variously described conditions has only occasionally been commented upon and the "common denominator" amongst them has not been well defined.

The present paper presents a preliminary report together with some comments arising from the study of 10 Italian families and of 1 Italian bachelor (comprising altogether more than 50 individuals) all affected with what is believed to be a similar condition, but of varying degrees of intensity. In addition, blood smears of 60 consecutive individuals of Italian origin were examined for oval, target and stippled red cells.

Case Reports. I. *Caruso Family—Hypochromic Anemia, Marked Splenomegaly, Acholuric Jaundice, Marked Bone Changes, Target, Oval, Stippled Red Cells, Increased Hypotonic Resistance.* The patient, a young man of Italian parentage, had been pale since infancy. Physical development had been normal and when examined at the age of 20, he was found to be tall and well formed. There was a suggestive Mongoloid appearance of the face, icterus of the sclerae, moderate pallor, marked splenomegaly, and a rough blowing systolic murmur heard over the entire precordium. A well-defined hypochromic anemia with many target cells was present. Elliptical and stippled red cells were common, but no nucleated red cells were found. The evidences of greatly increased blood destruction were present (bilirubinemia of the "indirect" type, greatly increased output of fecal urobilinogen), together with the bone marrow findings of intense erythroblastic hyperplasia. There were generalized bone changes, quite similar to those seen in Cooley's anemia. The patient's age, normal physical development, and lack of nucleated erythrocytes in the peripheral blood served to differentiate this case from those of typical Cooley's erythroblastic anemia. The patient's family was unusually uncooperative and it was impossible to do complete studies. However, from the few studies made, a familial abnormality was apparent (Table 5). Although the father,

the mother and one of two sisters studied were apparently in good health, they showed definite numbers of target, oval and stippled red cells

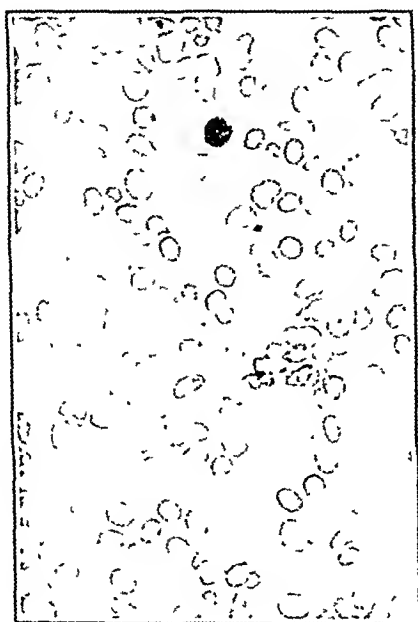


FIG. 1.—Photomicrograph of blood smear ($\times 520$) of a case of outspoken Cooley's anemia (P. W.) prior to splenectomy. There is great diversity in cell size with both microspherocytes and macrocytes, an occasional nucleated red cell and an occasional target cell. The marked evidences of blood destruction were present.

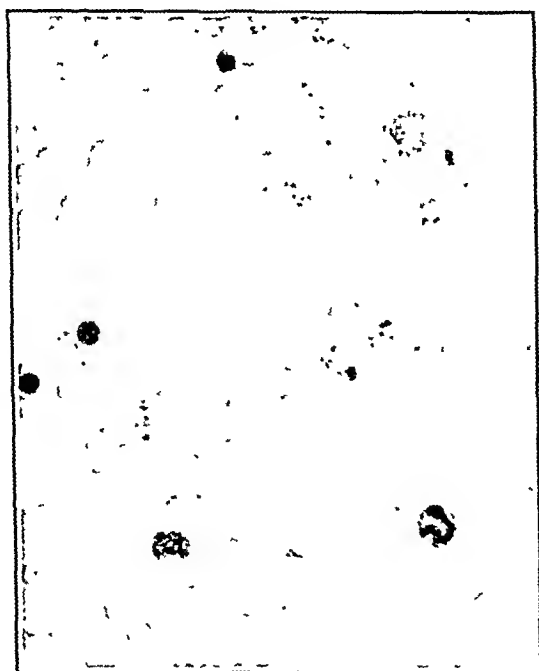


FIG. 2.—Photomicrograph of blood smear ($\times 520$) of a case of Cooley's anemia (P. W.) following splenectomy. The target cells have greatly increased in number, as have the nucleated red cells. In addition there is less spherocytosis and the evidences of increased blood destruction have almost completely disappeared.

TABLE 1. PENNELLO FAMILY—HYPOCHROMIC ANEMIA, SPLENOMEGALY, NO BONE CHANGES, ACHOLURIC JAUNDICE, TARGET, OVAL, STIPPLED RED CELLS

	Age	Hgb. (%)	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retes. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./100 cc.)	Spleen	Heart murmurs
Grandfather (mat.)	81	82	3 79	6,900	470	0 5	105	None	None	None	44-12	0 5	..	None
Dominic Biscetti	53	60	3 56	6,100	311	5 0	90	0 7	5 0	2 5	42-20	0 8	Just palpable	None
Grandmother (mat.)	37	53	4 10	5,200	482	3 0	79	2 9	4 6	1 7	38-12	2 7	2-3 f.b.	None
Mother	37	100	5 01	10,500	802	1 0	90	None	None	None	44-20	0 9	None	None
Father Felix	17	77	1 86	9,100	504	2 4	80	2 0	4 6	1 4	44-12	3 5	2 f.b.	None
Children Vincent	15	65	4 89	10,800	721	2 0	80	1 2	1 9	2 1	40-16	1 7	1 f.b.	None
Mary	13	100	5 08	9,000	101	None	None	..	42-24	..	None	Rough systolic
Rose	11	62	4 47	10,300	653	5 0	80	3 6	1 2	4 1	36-12	6 0	1-2 f.b.	and diastolic
Anthony	7	59	1 88	12,000	714	5 3	61	3 4	1 5	4 4	42-12	0 7	2 f.b.	Rough systolic
Phyllis	6	58	1 40	12,300	616	6 6	73	2 8	1 5	4 3	42-16	2 8	2 f.b.	Rough systolic
Felix	4	60	5 61	13,100	561	2 2	59	4 6	2 3	2 0	38-08	0 2	1 f.b.	None
Dominic	2	74	5 13	11,300	877	2 2	65	0 6	0 4	None	40-20	1 7	1 f.b.	None

TABLE 2.—LUCCIO FAMILY—HYPOCHROMIC POLYCYTHEMIA, FREQUENT SPLENOMEGALY, OCCASIONAL JAUNDICE, OCCASIONAL HEART MURMURS, RETICULOCYTOSIS, TARGET, OVAL, AND STIPPLED RED CELLS, NO BONE CHANGES

	Age	Hgb. (%)	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retes. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./100 cc.)	Spleen	Heart murmurs
Father Angelo	53	74	5 49	5,200	467	2 4	71	2 3	2 8	0 5	38-08	1 2	4 f.b.	None
Mother Jennie	35	Not studied	80	1 5	3 9	1 2	46 16	1 0	2-3 f.b.	None
Children Louis	31	88	6 01	7,700	80	1 5	3 9	1 2	46 16	1 0	2-3 f.b.	None
Sarno	29	Not studied	80	1 5	3 9	1 2	46 16	1 0	2-3 f.b.	None
Connie	27	Not studied	80	1 5	3 9	1 2	46 16	1 0	2-3 f.b.	None
Rose	25	Not studied	80	1 5	3 9	1 2	46 16	1 0	2-3 f.b.	None
Anne	23	65	5 14	7,200	491	1 2	70	3 0	1 8	1 0	38-08	0 2	Not felt	None
Josephine	23	65	5 14	7,200	491	1 7	74	None	Tend. ency	None	44-26	1 4	Not felt	None
Antonietta	22	90	5 76	7,400	519	..	74	3 5	3 9	0 1	40-12	0 6	Not felt	None
Agnes	20	62	6 27	8,300	76	3 4	7 1	0 7	40-12	0 6	Not felt	None
Carmela	18	78	5 64	9,100	76	3 4	7 1	0 7	40-12	0 6	Not felt	None
Mary	16	Not studied	76	3 4	7 1	0 7	40-12	0 6	Not felt	None
Louise	12	Not studied	76	3 4	7 1	0 7	40-12	0 6	Not felt	None
Grandchildren (children of Sarno)	7	68	5 45	20,700	572	1 0	70	2 1	2 0	0 5	36-08	0 7	3 f.b.	Rough systolic
Richard	4	60	5 60	9,000	1500	1 2	68	1 3	2 3	1 9	40-12	0 8	Not felt	Rough systolic

II. *Perriello Family*—*Hypochromic Anemia, Splenomegaly, No Bone Changes, Acholuric Jaundice, Target, Oval, Stippled Red Cells*. This rather large Italian family consisting of father, mother, grandparents, and 8 children was quite coöperative. The mother was referred for study because the diagnosis of congenital hemolytic jaundice had been made in 2 of her children.

In general, the children had developed fairly normally, although 2 were undersized, and 1 was chronically hospitalized for rheumatic heart disease. Three of the children had recently, within a period of 2 weeks, developed nausea, fever, increasing pallor and jaundice. The mother, despite the birth of 8 children in 17 years, considered herself to be in moderately good health, and was able to carry on all the various household duties without assistance.

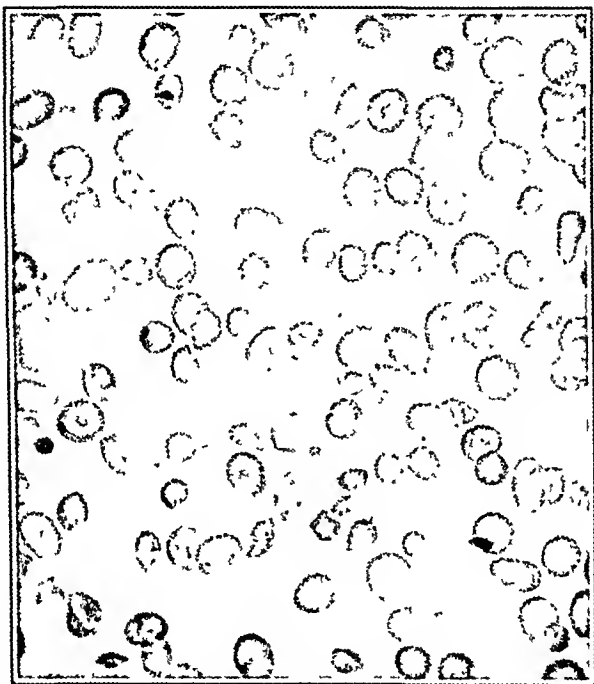


FIG. 3.—Photomicrograph of blood smear ($\times 560$) of a case of severe target cell anemia (J. Caruso) showing many target cells (with central dark spots), much anisocytosis, but no nucleated red cells.

The various physical and hematologic data are arranged in Table 1. Inheritance appeared to be through the grandmother (Bisesti) to the mother, Caroline, both the grandfather and the father being hematologically normal. Slight pallor, slight to moderate splenomegaly, and slight to moderate jaundice were usually present. A Mongoloid appearance of the facies was not apparent. Hypochromic anemia of mild to moderate degree associated frequently with slight acholuric jaundice was present in 7 of the 8 children, although in at least 1 instance (Felix, Jr.) hypochromic "polycythemia" was present. A diminished corpuscular volume, reticulocytosis, increased numbers of target cells, many oval and elliptical cells, and many stippled red cells were present. The resistance of the red cells to hypotonic salt solutions was definitely increased, especially in the "minimal" phase. An increased fecal urobilinogen output (indicating increased blood breakdown) and erythroblastic hyperplasia of the marrow were present in the cases studied. Slight osteoporotic changes, particularly noticeable in the metacarpal bones, were occasionally present. An unusual feature was the presence in 4 of the children (Rose, 13; Anthony,

TABLE 3. CONICO FAMILY. HYPOCHROMIC POLYCYTHEMIA WITHOUT ICTERUS, SPLENOEGALY, OR BONE CHANGES; TARGET CELLS, OVAL CELLS, SUPPLIED CELLS, INCREASED RESISTANCE

	Age	Hgb. %	R.B.C. (mill.)	W.B.C. (thous.)	Platelets (thous.)	Retes. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Supplied cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./ 100 cc.)
Father	33	88	1.73	7,500	517	1.5	90	None	None	None	42-21	0.6
Mother, Marie	31	69	5.95	9,200	612	4.3	60	1.2	4.3	2.2	42-12	1.2
Mother's brother, Vincent	27	82	6.78	10,200	511	1.9	60	5.2	1.2	1.5	38-12	0.3
Mother's sister, Josephine	32	68	5.82	5,100	686	1.1	65	36-12	0.7
Letitia	14	68	5.85	14,000	1112	4.0	60	0.9	2.7	0.9	42-16	0.7
Rose Marie	9	82	1.21	7,100	568	1.7	97	None	None	None	42-22	0.7

TABLE 100. VASIZANO FAMILY. HYPOCHROMIC POLYCYTHEMIA WITHOUT SPLENOEGALY, HEART MURMURS OR JAUNDICE, MOSTLY ELLIPTICAL AND OVAL CELLS WITH SOME TARGET CELLS

	Age	Hgb. %	R.B.C. (mill.)	W.B.C. (thous.)	Platelets (thous.)	Retes. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Supplied cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./ 100 cc.)
Grandmother (Zoffante), Mary	62	71	6.13	16,300	316	..	72	Few	Many	Few	31-12	0.2
Grandfather, Joseph	62	96	1.99	7,100	None	None	None	31-12	0.2
Mother, Theresa	43	71	5.78	10,600	607	1.3	61	0.5	17.5	1.7	31-12	0.8
Father	Not studied											
Children, Vincent	17	71	5.77	6,100	60	0.9	8.9	0.3	31-12	0.2
Arnand	6	69	5.76	9,300	60	1.3	2.8	0.6	31-12	0.2

TABLE 101. VASIZANO FAMILY. MARY ZUFFANTE—COURSE OF HEMOGLOBIN AND RED CELL COUNT

Date	Hgb., %	R.B.C., (mill.)	W.B.C., ..	Platelets (thous.)	M.C.V., (c. micra)
8-22-34	71	6.13	..	316	72
5-5-36	80	5.90
10-1-37	82	..	16,300
1-9-39	72	5.57
3-3-40	72	1.97	10,100
1-23-41	77	1.66

11; Phyllis, 7; and Edward, 6) of rough, blowing systolic murmurs. Rose had been diagnosed as a case of rheumatic heart disease and was confined to a chronic hospital. In the cases of Anthony, Phyllis, and Edward, who

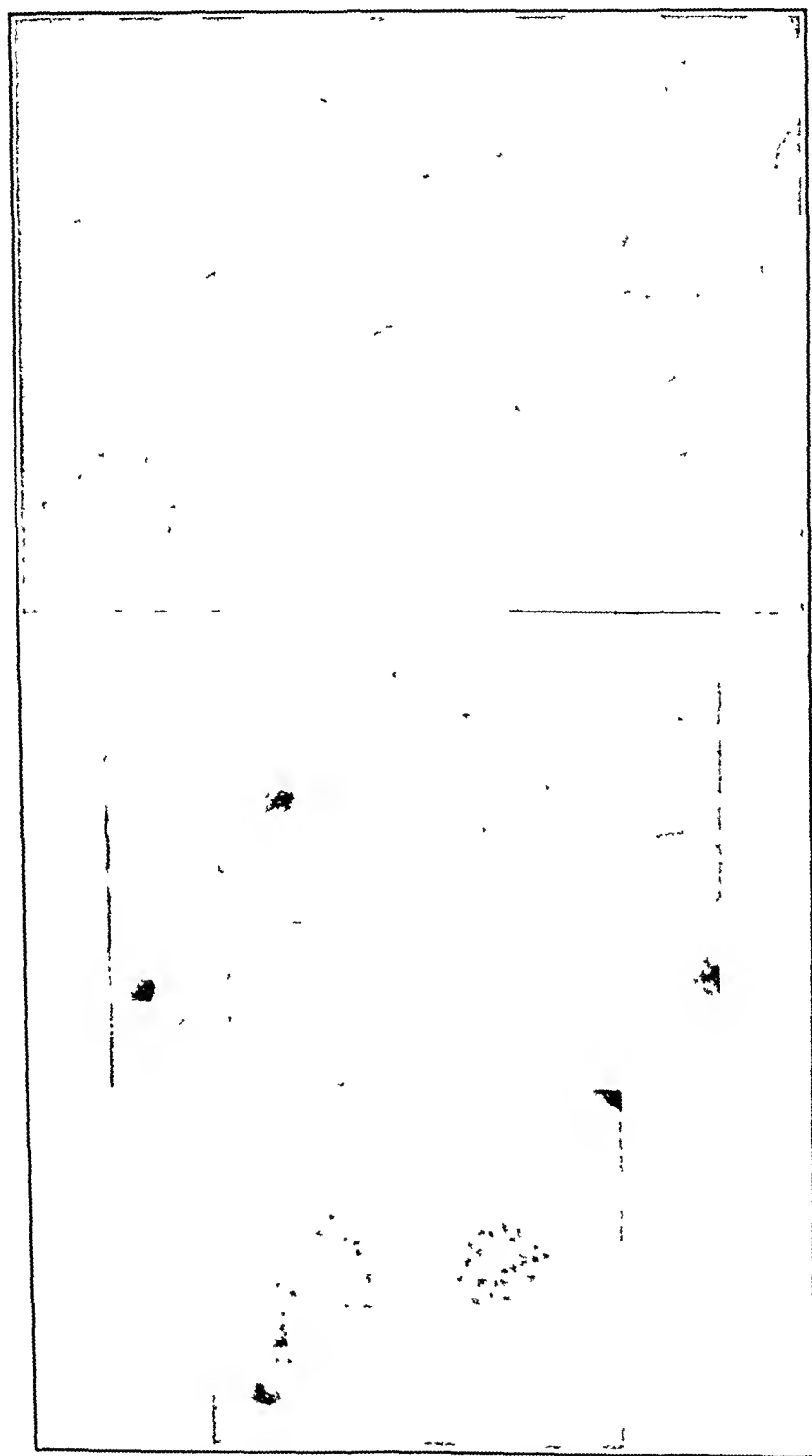


Fig 4 — Photomicrographs of blood smears ($\times 2000$) of a case of moderately severe target cell anemia (Phyllis Perriello) showing target cells and the very heavily stained stippled red cells characteristic of the condition.

were apparently in excellent good health and gave no history even suggestive of rheumatic fever, loud rough blowing systolic murmurs were present which became accentuated with exercise and did not disappear with change in position. Teleroentgenograms failed to disclose either cardiac enlarge-

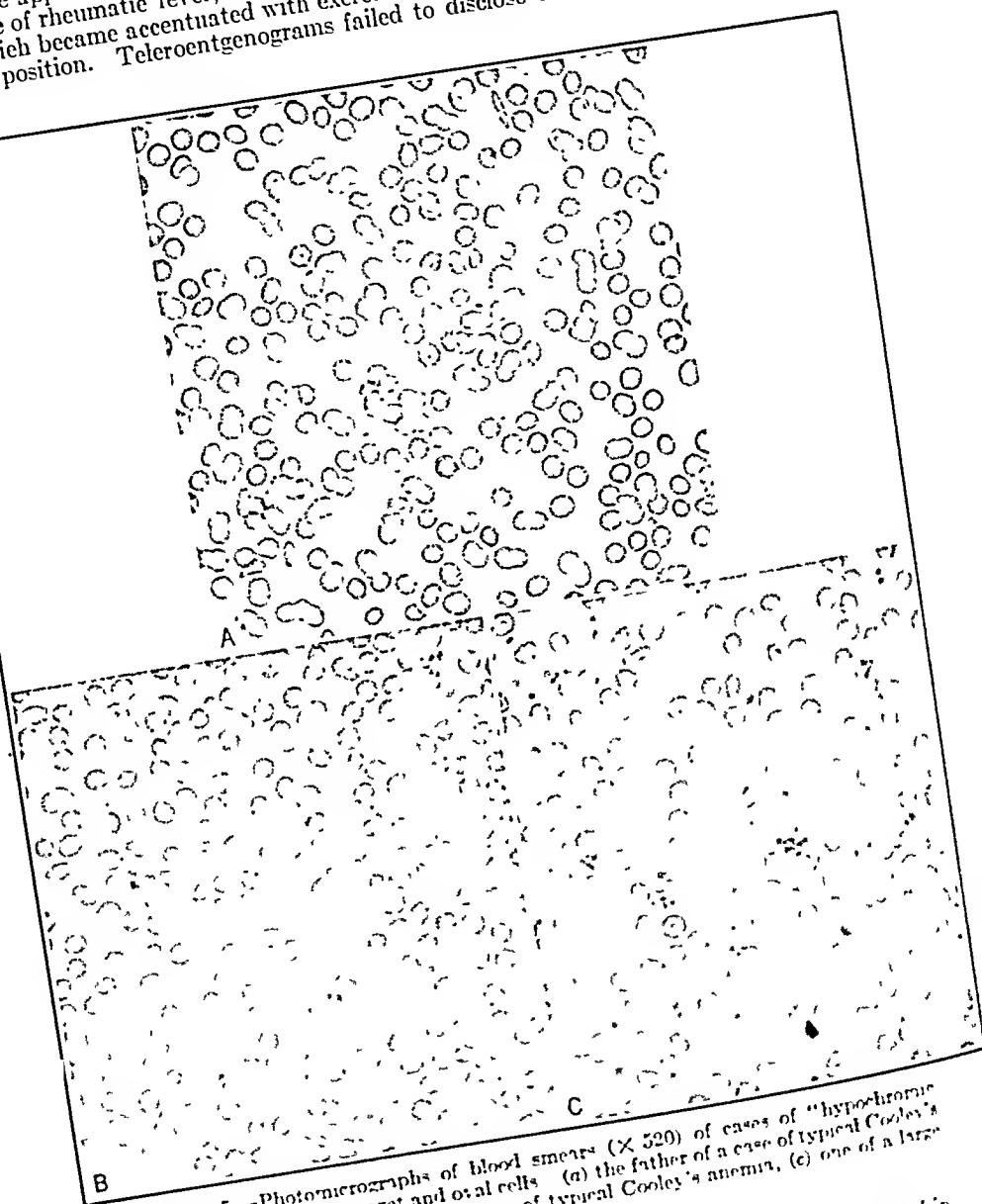


FIG. 5.—Photomicrographs of blood smears (X 520) of cases of "hypochromic polycythemia" with target and oval cells: (a) the father of a case of typical Cooley's anemia, (b) the sister of another case of typical Cooley's anemia, (c) one of a large family (Luce) with similar hematologic pictures.

ment or a bulge in the region of the pulmonary conus. The hemoglobin values (59%-62%) did not appear sufficiently low to result in "Lemic" murmurs. Similar murmurs were found in 2 of the grandchildren of L. family (see below). Treatment with iron, liver extract, vitamin B complex, riboflavin, and spleen extracts was completely ineffective.

III. *L. Family*—*Hypochromic Polycythemia, Frequent Splenomegaly, Occasional Jaundice, Occasional Heart Murmurs, Reticulocytosis, Target, Oval, and Stippled Red Cells, No Bone Changes.* This large Italian family consisting of mother, father, 11 children and 6 grandchildren was only slightly coöperative, and complete studies could not be made. The mother complained of almost constant headaches, and several of the children complained of "lack of pep" and pallor. In general, however, their development had not been retarded and they considered themselves to be in good health. Three of the children had been treated at one time or another for anemia. Inheritance in this family appeared to be through the mother. Of 5 children studied, 4 were affected. One of the male children (Sarno) had 2 children and both showed the characteristic features of the disease, their mother being completely normal. A Mendelian dominant type of inheritance thus appeared to be present. All of the affected individuals showed a normal physical development and a normal facies without evidence of "mongoloidism." There was slight pallor in several cases, borderline icterus in 2 cases, and splenomegaly in 3 of 8 cases examined. Hema-

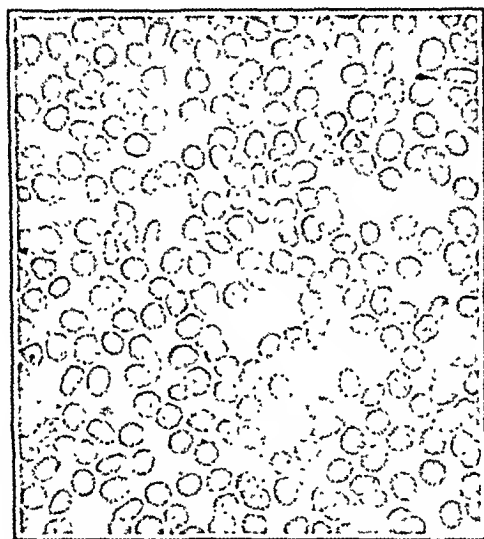


FIG. 6.—Photomicrograph of blood smear from a mild case of hypochromic anemia (Mariello) with target and oval cells.

tologically, "hypochromic polycythemia" (low hemoglobin values in the presence of a high red cell count) was the rule, and was associated with a greatly reduced mean corpuscular volume, slight reticulocytosis, and the presence of target, oval, and stippled red cells (Table 2). No nucleated red cells were seen. Increased hypotonic resistance was a constant finding. Slight bilirubinemia (above 1 mg. per 100 cc.) was present in the mother and 1 of the children (Sarno) had previously had slight jaundice. In 1 of the grandchildren (Richard, aged 7) there was a definite increase in the daily fecal urobilinogen output, indicating increased blood destruction despite the normal blood bilirubin value of 0.7 mg. per 100 cc. Roentgen rays of the skull and of the metacarpal bones in 4 cases were normal. Examinations of the bone marrow were not made. As in the P. family above, 2 of the grandchildren (children of Sarno) showed loud, rough, blowing systolic murmurs heard best in the apical region and along the left border of the sternum, and accentuated with exercise; there was no increase in the size of the cardiac silhouette. Treatment of selected members of the family with large doses of iron liver extract, yeast concentrate tablets, and ribo-

flavin both singly and in combination were completely without effect, the hemoglobin concentration remaining singularly constant from week to week.

IV. *Corrao Family; Veneziano Family; Danubio* (cf. also *Adorno Family* [Cooley's Anemia]—*Father and Pauline*)—*Hypochromic Polycythemia Without Icterus, Splenomegaly, or Bone Changes; Target Cells, Oral Cells, Stippled Cells, Increased Hypotonic Resistance.* *Corrao Family*—A daughter (Loretta), aged 11, was referred for study of anemia which had been discovered 2 years previously in the course of a routine blood examination prior to tonsillectomy. Despite the continued use of iron therapy during the period of 2 years, no change in hemoglobin had occurred. The child was otherwise quite healthy, although occasionally she became somewhat pale and nauseated. The mother (Marie Blonda Corrao) had always been well except for mild headaches in the past 2 years. A low hemoglobin value had also been discovered in her case 3 years previously while she was in a hospital preparing for a minor gynecologic operation. One of the mother's sisters was known to be anemic and a brother (Vincent Blonda) had recently been told that he had a low hemoglobin value. The father was in good health. One of the mother's maternal uncles, 1 of her maternal aunts, as well as other members of the maternal grandmother's family had been treated for anemia. Study of these cases is now in progress. The mother, who appeared quite healthy, showed fairly numerous telangiectatic blood-vessels over the cheeks. The brother, a strapping young man of 27, seemed in excellent health. Loretta, the patient referred to above, was somewhat sallow but not definitely pale; her sister Rose Marie was healthy in appearance. None of these individuals showed icterus, hepato- or splenomegaly, or cardiac murmurs. However, the blood (Table 3) showed very similar findings of hypochromic polycythemia with target cells, oval cells, stippled cells, reticulocytosis, and increased hypotonic resistance in the mother, her brother and the child Loretta. There was no bilirubinemia. Normal hematologic findings were present in the father and the child Rose Marie. Inheritance was thus dominant and through the mother.

Veneziano Family—Theresa, the mother, aged 43, complained of numerous symptoms (backache, pain in the legs, etc.) and on routine blood examination was found to have a low hemoglobin value, but an elevated red cell count. Her mother was known to be anemic, and her mother's mother had probably been anemic. The patient had advised against immigration to and because of this a physician in Italy had advised against immigration to this country. At the ages of 18 and 32 she had been treated for anemia with both iron pills and iron injections. With each childbirth anemia was found and she was given iron. The patient's mother and 2 of her 3 children were examined. The mother (Mary Zuffante, aged 62) had been a patient of the Boston Dispensary since 1931 for numerous complaints centering chiefly around the heart and stomach. She was at first considered to have neurasthenia and later "secondary" anemia. Further studies showed low hemoglobin values in association with elevated red cell counts and in 1931 she was thought to have "polycythemia with hypochromic anemia." Treatment with iron caused diarrhea. The hereditary nature of her condition was first noted in 1938 by Dr. H. Brugch who believed she had "hereditary benign polycythemia with elliptical red cells." In the last year or two there had been increasing cardiac decompensation and a progressive fall in the red cell count from the levels above 6 million to levels below 5 million (Table 4 b). The hemoglobin values remained essentially constant.

Of the patient's 3 children, Vincent, aged 15, also had "stomach trouble," for which no cause could be found. Armand felt well. Examination of these individuals was consistently negative, and there was no evidence of anemia, icterus, hepato- or splenomegaly, or cardiac murmurs. The hematologic findings in the patient, her mother, and the 2 children examined were very similar, showing hypochromic polycythemia, very low mean corpuscular volumes, very slight reticulocytosis, and target, oval and stippled red cells with increased hypotonic resistance (Table 4 a). First

preparations of the patient's blood showed questionable sickling. Treatment with iron was ineffective. Further studies could not be made because of the family's lack of cooperation.

Danubio—the patient, aged 48, a bachelor, born in Italy, complained of a heavy sensation in the head which had prevented him from working during the past 15 years. He had consulted many physicians and in the course of one study had been found to have "polycythemia," for which phenylhydrazine had been prescribed. With the exception of 1 brother and a nephew, no relatives were available for study. Repeated examinations of the patient showed only numerous telangiectases of the face, the buccal mucous membranes and the nail beds. There was no icterus, hepato- or splenomegaly. The brother and his child showed no abnormalities, either physically or hematologically. Numerous blood examinations gave hemoglobin values of 75%–85%, red cell counts of 6.01 to 6.93 million, slightly elevated leukocyte counts (13,500 to 14,500), normal platelet counts, slight elevation in reticulocytes to approximately 2.0%, very low mean corpuscular volume, no bilirubinemia, and the presence of many target cells with occasional oval and stippled cells and increased hypotonic resistance of the red cells. There were no bone changes; the bone marrow showed erythroblastic hyperplasia. The fecal urobilinogen output and the total blood volume were normal. Treatment with iron, liver extract, and large amounts of spleen extracts were completely without effect on the blood counts and on the patient's symptoms (which were almost certainly neurasthenic in origin).

V. Mariello Family—Mild Refractory Hypochromic Anemia Without Icterus or Splenomegaly and With Target, Oval, and Stippled Red Cells. The mother, aged 58, was referred because of hypochromic anemia which had failed to respond to iron. She had but few complaints and physical examination was entirely negative. Although she had 9 children, only 1, Anthony aged 15, was sufficiently cooperative to be examined. He had no complaints and on examination showed no pallor, icterus, hepato- or splenomegaly, or cardiac murmurs. The hematologic findings in mother and son were strikingly similar: slight hypochromic anemia, diminished mean corpuscular volume, and the presence of target, oval, and stippled red cells with increased hypotonic resistance.

VI. Unselected Italian Individuals. The blood smears of 60 unselected individuals of Italian parentage who came to the Medical Clinic for various conditions were studied for the presence of target, oval, and stippled cells. In 8 (13%), definite and unequivocal changes in the red cells were apparent. Of these, 3 showed target cells, oval cells, and stippled cells in definite numbers; in 5, ovalocytosis of definite degree was apparent either with or without stippling. Further studies of unselected Italians are being made in the course of which more definitely quantitative values regarding "leptocytosis" and ovalocytosis, etc., will be obtained.

Comment. 1. *The Fundamental Unity of the Various Target Cell Syndromes, Including Cooley's Anemia.* From study of these cases it is possible to arrange in a descending scale, beginning with the outspoken and well-known although rare Cooley's anemia, various more frequently encountered hereditary syndromes, which present as their common denominator a reduction in the hemoglobin level, hypochromia, abnormalities of the red cells including the presence of target cells, oval cells, stippled cells, increased hypotonic resistance and complete refractoriness to iron therapy. At the lower end of the scale are individuals without anemia or evidence of other abnormality but showing increased numbers of target or oval cells (Table 6).

This arrangement of the various syndromes indicates possible relationships among them. That this is probable is indicated by the following: (1) Certain siblings and *both* parents of the cases of Cooley's anemia studied showed the hematologic changes of mild Mediterranean target cell syndrome, usually hypochromic polycythemia. (2) The various groups merged into each other by insensible transitions. (3) Individuals of the same families occasionally showed the same variations as were noted in the groups. These considerations indicate that Cooley's anemia is probably the most severe manifestation of an hereditary disorder occurring in people of Mediterranean origin and in which target cells and increased hypotonic resistance are prominent features.

2. *Heredity.* In the families in which one of the milder syndromes was present, inheritance was present as a simple dominant mechanism, occurring through either parent. This is well brought out in the Periello, Luccio, and Veneziano families, in which members of three generations were available for study. Seven of the 8 Periello children and 4 of the 5 Luccio children studied were affected, although in different degrees. In the Periello family, the transmitter was evidently the grandmother (Bisesti) who showed a very mild condition of hypochromic anemia with elliptical and target cells. Her daughter (the mother Caroline) showed a much more severe condition with jaundice and splenomegaly and the latter's children were similarly affected. The male grandparent and parent were both completely normal. In the Luccio family, the grandmother, the son Sarno, and the latter's children all showed hypochromic polycythemia with target, oval and stippled cells; the grandfather and daughter-in-law were both normal.

In the families of the 4 severe cases studied—3 of typical Cooley's anemia and 1 of the "anerythroblastic" type—*both* the father and the mother showed a mild target-oval cell syndrome. What is more, a mild Mediterranean disorder was often present in certain of the siblings of the cases of Cooley's anemia (Table 5). This suggests that the mild disorder is readily transmitted as a Mendelian dominant, but that the severe disorder requires the presence of homozygous genes. The exact nature of the hereditary process remains to be worked out and will be the subject of another report.

3. *Pathogenesis.* A few comments may be ventured at this time regarding possible pathogenesis. The hypochromia, the very low mean corpuscular volume, and the complete lack of response to iron medication suggest a disturbance in the hemoglobin metabolism, more particularly perhaps in the development of a normal complement of hemoglobin in the cytoplasm of the nucleated red cells in the bone marrow. This may be reflected by the development of unusually thin mature red blood cells (target cells and oval cells). Red cell formation is itself probably undisturbed since there is erythroblastic hyperplasia of a normal (normoblastic) type and the red cell count in the peripheral blood is frequently greater than normal. The presence of large numbers of stippled red cells sug-

gest a possible "toxic" effect on the developing red cell; however, this seems unlikely in view of the hereditary nature of the process, and may be further evidence of an abnormal hemoglobin metabolism. Of particular interest in the more severe cases is the presence of increased hemolysis, of which the cause is at present obscure. This may be due either (1) to an increased breakdown of hemoglobin precursors which cannot properly be metabolized; (2) to a possible increased *in vivo* fragility of the target cell, although *in vitro* it has an increased resistance to hypotonic salt solutions, or (3) to some abnormality in the spleen. Combinations of these factors are also possible. Coincidentally with increased blood destruction are present certain evidences of increased blood regeneration: reticulocytosis, leukocytosis in some cases, and perhaps basophilic stippling. The high red cell counts in many of the cases suggest an attempt on the part of the marrow to compensate for the hemoglobin deficiency. All that can be stated at present is that the disorder—whether mild, moderate, or severe—is an inherited one in which the red cells are abnormally thin ("leptocytosis") and the hemoglobin production abnormal.

TABLE 5.—HEREDITARY NATURE OF 4 SEVERE CASES ("COOLEY'S ANEMIA") IN 4 FAMILIES SHOWING MEDITERRANEAN TARGET-OVAL CELL DISEASE

	Hgb.	R.B.C.	Hypotonic fragility	Target cells %	Oval cells %	Type of case
MERCURIO FAMILY						
Father (John)	85	6.73	.34-.16	0.2	2.5	Hypochromic erythrocytosis with oval cells
Mother (Mary)	84	6.66	.36-.16	0.2	4.6	Hypochromic erythrocytosis with oval cells
John, Jr.	77	5.56	.38-.20	1.0	1.7	Hypochromic erythrocytosis with oval cells
Irene	88	4.98	.42-.24	0.2	0.2	Normal
Helen Marie	24	2.24	.38-.16	2.4	8.4	Cooley's anemia
WHIBY FAMILY						
Father (Joseph)	85	5.50	.38-.12	8.6	0.9	Hypochromic erythrocytosis with target cells
Mother (Freda)	74	5.40	.36-.08	4.9	0.5	Hypochromic erythrocytosis with target cells
Philip	21	1.77	.44-.12	1.2	5.8	Cooley's Anemia
ADORNO FAMILY						
Father (Frank)	75	5.24	.40-.16	2.6	1.6	Hypochromic anemia with target and oval cells
Mother (Lucy)	74	4.88	.40-.16	Hypochromic anemia with target and oval cells
Vincent	24	2.05	.36-.04	Many	Many	Cooley's anemia
Pauline	75	6.20	.38-.12	1.3	2.8	Hypochromic polycythemia
Frank, Jr.	Normal
CARUSO FAMILY						
Father (Orario)	80	4.97	.42-.12	1.3	1.3	Hypochromic anemia with target and oval cells
Mother (Anna)	71	4.29	.38-.12	1.5	0.5	Hypochromic anemia with target and oval cells
Lucy	87	4.36	.42-.16	None	None	Normal
Mary	68	4.72	.38-.12	3.4	1.2	Hypochromic anemia with target and oval cells
Joseph	50	5.12	.44-.04	52.0	Many	Anerythroblastic Cooley's anemia—target cell anemia

4. *Certain Features of Diagnostic Significance.* Study of the cases presented in this paper has indicated that the presence in people of Mediterranean origin (Italians, Greeks, and Syrians) of a low hemoglobin value, a low color index, or a hypochromic type of

polycythemia should immediately bring to mind a possible target cell disorder. In cases of splenomegaly, particularly if they are familial; in cases of possible congenital hemolytic jaundice in Italians; and in various other types of hemolytic syndromes in the same racial group, the question of a target-oval cell syndrome should be thoroughly investigated. The presence of a systolic cardiac murmur in an Italian child may indicate target cell anemia rather than rheumatic heart disease. Likewise, basophilic stippling, when present in an Italian worker exposed to lead, although suggestive of lead poisoning may be indicative of a target cell syndrome; this may occasionally be of medico-legal significance. The diagnosis of sickle cell anemia in a white person of Mediterranean origin should be thoroughly investigated, since occasional cases of target-oval cell syndrome show an unusual degree of elliptocytosis. However, that true cases (transitional forms?) of predominantly African sickle cell anemia occur in Mediterranean individuals is certain.

The diagnosis of one of the target cell syndromes is based upon (a) the racial factor, (b) a reduction in hemoglobin concentration in association with a low color index, (c) refractoriness to iron therapy, (d) the presence of increased numbers of target cells and reticulocytes, usually in association with oval and stippled red cells, (e) the presence of increased hypotonic resistance of the erythrocytes, and (f) the absence of such conditions as hepatic disease, steatorrhea, bleeding, or lead poisoning. Target cells and increased hypotonic resistance of the red cells may be present in the two former conditions, which should, however, show the various associated collateral features. In the presence of hypochromic anemia with reticulocytosis, bleeding should always be investigated and may only be found by careful examinations of the stools for occult blood. This is particularly true if the hypochromic anemia does not respond to iron therapy. In certain cases, lead poisoning may have to be ruled out.

A high familial incidence will almost always be found in a given instance if this can be investigated. Whether icterus, splenomegaly, bone changes, cardiac systolic murmurs and nucleated erythrocytes are present depends upon the severity of the condition (cf. Table 6). The exact type of syndrome present—whether refractory hypochromic anemia, hypochromic polycythemia, hemolytic target cell jaundice with splenomegaly, etc.—usually depends upon the family affected, since hypochromic polycythemias appear to beget hypochromic polycythemias, unless both parents happen to be affected in which case a more serious disorder may ensue.

5. *Possible Relationship of the Mediterranean Target Cell Syndrome to the (African) Sickle Cell Syndromes.* An outstanding hematologic feature in a case of sickle cell anemia is the presence of large numbers of target cells. In fact, target cells are frequently more conspicuous in a stained preparation than are sickled cells. Sickle cell anemia, although hemolytic, is almost always accompanied with increased hypotonic resistance of the red cells, particularly in the

"minimal" phase. As with the Mediterranean target-oval cell disease, various gradations in the broad syndrome of sickle cell anemia may be discriminated, ranging from (a) the mild "sickle cell trait" brought out only in fresh preparations to (b) hypochromic anemia with many target cells and only occasional sickled cells to (c) hypochromic anemia with splenomegaly, icterus and frequently cardiac systolic murmurs, and finally to (d) the outspoken sickle cell anemia with marked sickling in the peripheral blood, reticulocytosis, stippling, target ovals and nucleated red cells. In such cases, nucleated red cells may be so abundant that the designation "erythroblastic anemia" may be as applicable as in Cooley's anemia.

TABLE 6.—FAMILIAL MEDITERRANEAN TARGET-OVAL CELL SYNDROMES

Anemia		Jaundice	Splenomegaly	Bone changes	Nucleated R.B.C.	Target, oval, stippled cells	Hypotonic fragility	Response to Fe treatment
Cooley's erythroblastic anemia	Severe hypochromic	++	+++	+++	++	+	Incr. resist.	None
"Target cell anemia" (adult erythroblastic type of Cooley's anemia)	Moderate	++	++	++	-	++	Incr. resist.	None
Congenital hemolytic target cell jaundice	Slight to moderate hypochromic	+	+	±	-	++	Incr. resist.	None
Hypochromic polycythemia with splenomegaly and target and oval cells	Hypochromic polycythemia	±	±	-	-	++	Incr. resist.	None
Hypochromic polycythemia with target and oval cells	Hypochromic polycythemia	-	-	-	-	++	Incr. resist.	None
Hypochromic anemia with target, oval, and stippled red cells	Slight hypochromic	-	-	-	-	+	Incr. resist.	None
"Congenital lepto- and elliptocytosis"	None	-	-	-	-	+	Incr. resist.	None

All of these features parallel closely those of the various Mediterranean syndromes. Since the thin target cell is found in both conditions, and since ovalocytosis, elliptocytosis, and meniscocytosis (sickling) may also be indicative of increased thinness, it is possible that the two types of syndromes are closely related. Viewed in this light, various transition forms between the two conditions may be expected.

Recently, Dr. Moises Chediak of Havana informed me of the case of a Cuban family in which 3 children developed a hematologic disturbance. Generations previously, the family, of pure Spanish stock, had emigrated from the Canary Islands. One child developed idiopathic thrombopenic purpura with slow recovery after transfusions. A second child who developed anemia, jaundice, and splenomegaly showed the typical hematologic features of sickle cell anemia although the facies was Mongoloid in type and Roentgen rays of the bones were characteristic of Cooley's anemia. A third child presented hypochromic anemia refractory to iron therapy; after 2 years of observation, sickled cells were noted in wet preparations. The possibility exists that in this family of Mediterranean origin, a transitional condition with the features of both sickle cell anemia and target cell anemia may be present. In an Italian girl

studied at the New Haven Hospital (the records were made available to me through the kindness of Dr. Arthur Geiger) in whom the diagnosis of sickle cell anemia was made, various familial, hematologic, and roentgenologic features of a Mediterranean syndrome of moderate severity were present. Recently, a typical case of Cooley's erythroblastic anemia in a negro child was observed at the Mt. Sinai Hospital of New York. All the various hematologic and bone changes were present and repeated examinations of the blood for sickling were always negative.

Further studies of the possible relationship between these two conditions, one occurring predominantly in Mediterranean peoples and the other in those of African origin, are now in progress.

6. *Terminology.* The matter of terminology for description of these syndromes is a difficult one. Use of the term "target cell anemia" may be criticized because target cells occur in such diverse conditions as hepatic disease, steatorrhea, following splenectomy, and to some extent with chronic hemorrhage. The same criticism may be made for erythroblastic anemia, and for other hematologic conditions which are described by the characteristics of the blood cell. The term Mediterranean anemia, although sufficiently vague, does not adequately describe the cases with a high erythrocyte count, although the hemoglobin level may be distinctly lowered. The numerous previous designations referred to in the introduction are also unsatisfactory for one cause or another. Since most cases occur in Mediterranean peoples and are familial, and since a common feature is the hypotonically resistant target-oval cell, I have thought it best to refer to these cases as "familial Mediterranean target-oval cell disease." This unwieldy term is admittedly unsatisfactory but must await revision as the pathogenic mechanisms are better understood.

7. *Course and Therapy.* Cooley's anemia, the most severe form of the target-oval cell syndromes, is almost uniformly fatal before the age of 12. The milder syndromes appear to run a protracted course without much effect on the general health. In those cases with jaundice and other evidences of increased blood destruction, there may be an enhanced tendency for the development of gall stones; this possibility has not as yet been investigated. The exact significance of the cardiac systolic murmurs heard in a number of the cases, especially in children, is thus far uncertain and must await long-term studies. In 1 of the cases of hypochromic "polycythemia," Mary Z. (Table 4b), the course of the anemia during a period of about 7 years from the ages of 55 to 62 could be followed. There was a gradual reduction in the red cell count from 6.15 to 4.66 million, the hemoglobin concentration remaining remarkably constant at between 72% and 82%. This probably indicates a gradual reduction in red cell formation with advancing years. The static quality of the hemoglobin level was noted in all the other cases which were followed.

The response to therapy is uniformly *nil*. Despite the low hemoglobin concentration and low color index, no response whatever to iron therapy occurs. This is about the only exception to the dictum that a hypochromic anemia always responds to iron therapy. Liver extract, various members of the vitamin B complex, splenic extracts, etc., are also completely ineffective. As already stated, the negative results with therapy rule out various deficiency syndromes, and with the hereditary nature of the disease, point to an inherited disturbance either in the hemoglobin metabolism or in red cell formation.

Summary. 1. In a previous paper, attention was directed to a condition tentatively called "target cell" anemia and representing a relatively mild form of Cooley's anemia. The chief hematologic feature was the presence of numerous target cells, which were unusually resistant to hypotonic solutions of sodium chloride.

2. Further studies of Italian families have revealed several syndromes of varying degrees of severity ranging from Cooley's erythroblastic anemia to conditions with mild hypochromic anemia, target, oval and stippled cells, and increased hypotonic resistance of the erythrocytes. These syndromes, inherited usually as a Mendelian dominant, showed a high incidence of transmission in the offspring. In the few cases of Cooley's anemia studied, *both* parents were affected with one of the milder types of syndromes.

3. In a person of Mediterranean (more particularly Italian) origin, the question of target cell anemia should be considered in the presence of splenomegaly, a hemolytic type of icterus, a cardiac systolic murmur, a reduction in hemoglobin, an elevated red cell count, anemia refractory to iron therapy, or stippling or elongation of the red cells. The diagnosis is substantiated by the presence of target, oval, and stippled red cells, increased hypotonic *resistance* of the red cells, and complete refractoriness to iron therapy.

4. The fundamental inherited abnormality appears to lie in a disturbance of the hemoglobin metabolism with the result that the nucleated red cells become deficient in and are likewise unable to take on their normal complement of hemoglobin. In consequence, thin and hypotonically resistant erythrocytes—target and oval cells—are produced. Basophilic stippling and refractoriness to iron therapy are probably concomitant abnormalities. The increased hemolysis in the more severe cases may be due to the breakdown of unused hemoglobin precursors.

5. The numerous resemblances between the essentially Mediterranean target cell syndromes and the essentially African sickle-cell anemia are pointed out. It is possible that the two conditions may be closely related entities with unusual erythrocytic thinness ("leptocytosis") as one of the fundamental abnormal traits. They are important, not only diagnostically, but because the mating of 2 individuals with a relatively mild condition may result in the appearance of either full-blown Cooley's anemia or sickle-cell anemia in the offspring.

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PRIMARY FRIEDLÄNDER PNEUMONIA

BY LEROY HYDE, M.D.

AND

BERNARD HYDE

NEW YORK, N. Y.

(From the Tuberculosis Service, First Medical Division, Bellevue Hospital)

Introduction. The Gram-negative bacillus which now bears his name was discovered by Carl Friedländer¹¹ in 1882. Friedländer believed that it was the chief cause of pneumonia, while a later opinion held that it was merely a secondary invader, after Sternberg²⁴ and Weichselbaum²⁶ showed the pneumococcus to be the most common cause of lobar pneumonia. Now it is known that the Friedländer bacillus is responsible for a small but definite percentage. The large series of Solomon²² (with review of literature to 1937), Bullova, Chess and Friedman,⁶ Solomon,²³ and Perlman and Bullova²⁰ indicate that Friedländer pneumonia is not rare. Solomon emphasized the chronic phase of Friedländer pneumonia and Muschenheim¹⁹ reported 1 patient who, within 3 years had 3 bouts of Friedländer pneumonia with necrosis and cavitation. Friedländer bacilli were present in this patient's sputum for at least 6 years.

The present report is based on 51 cases of Friedländer pneumonia from Bellevue Hospital and The New York Hospital. Five of the chronic cases were previously reported by Solomon,²³ but are included here because of the interesting follow-up observations. The acute and chronic cases are considered together, as separate study of them revealed no significant differences in age or sex incidence, the type of organism involved, blood response, seasonal incidence, the lobes involved, or symptoms. It would appear that acute primary Friedländer pneumonia can terminate with death, with complete fairly rapid recovery, or with parenchymal destruction (the chronic phase). The chronic Friedländer pneumonia is thus an end result rather than a separate entity.

Etiology. BACTERIOLOGY. 1. *Morphology.* Excellent bacteriologic descriptions of the short, Gram-negative, non-motile, and non-sporeing rods can be found in such textbooks as those of Gay¹² and of Topley and Wilson.²⁵ The thick capsules are easily stained.

2. *Cultural*. The Friedländer bacillus grows luxuriantly aërobically at 37° C. (range between 12 and 45° C.). Growth on agar is very characteristic, the colonies being large, gray-white, and very mucoid with a glossy, smooth, viscid surface. On a blood agar plate, the colonies are convex, milk-white, 1 mm. in diameter with a smooth surface. There is no hemolysis. Biochemical reactions are varied, because of different strains.

3. *Colony Variation*. As with other bacteria, mucoid, smooth, intermediate rough, and true rough types may be recognized. The mucoid colony (termed "s" or smooth by some workers) is the most important clinically, as this group contains organisms that are antigenic, with the specific soluble substance, and are pathogenic.

4. *Antigenic Structure*. The gummy capsule of the Friedländer bacillus is a nitrogen-free polysaccharide, containing glucose^{1,14} and about 92% water. The soluble specific substance of *B. friedländer*, type B, and of pneumococcus type II are closely related chemically. Both are dextrorotary and acidic. Friedländer bacillus, type B, capsular material is precipitated by barium hydroxide and neutral lead acetate, whereas pneumococcus type II capsular substance is not. They are thus not chemically identical, although the two capsular substances must be closely related. Sera of the former will protect mice against pneumococcus type II infection and *vice versa*. Horse sera are superior to rabbit sera in this respect. Heidelberger, Goebel, and Avery^{1,14} have suggested that the similar reactions of these two dissimilar organisms must be due to a "closely similar configuration of atoms in some portion of the complex molecule."

Julianelle¹⁶ divided the Friedländer bacilli into 3 serological types, A, B, and C, and a mixture, called X, specificity being based on agglutination, absorption, precipitin, and protection tests. Type specificity depends on capsular polysaccharide as with pneumococci. Later types D and E were described.²²

5. *Occurrence*. Friedländer bacilli have been found in the soil, air, dust, mud, and water. Experimentally the mouse is the most susceptible laboratory animal. Subcutaneous or intraperitoneal injections of 1:1 million or 1:1 billion dilutions of young cultures often kill mice in 1 to 3 days. In humans, Friedländer bacilli have been isolated from the respiratory tract, stools, urine, bile, meninges, vagina, and uterus.²

ETIOLOGIC FACTORS. 1. *Age*. Friedländer pneumonia is most likely to be found in males over 40 years of age (Table 1). Forty-five (88%) of the present series were between 41 and 84 years of age.

TABLE 1.—AGE INCIDENCE OF FRIEDLÄNDER PNEUMONIA

Age of patient, yrs.	No. of patients	Percentage
21-30	1	2
31-40	5	10
41-50	14	27
51-60	18	35
61-70	10	20
71-	3	6

SS
(over 40)

2. *Sex.* There were 43 males and 8 females, a ratio of more than 5:1 (Table 2).

TABLE 2.—AGE AND SEX INCIDENCE

Reported series	Total patients	Patients over 40 years		Sex		Ratio Male/ female
		No.	%	male	female	
Solomon, 1937 ¹	32	28	87.5	28	4	7:1
Bullowa, 1937 ²	41	29	70	36	5	7:1
Bullowa, 1941 ²	37	26	70	32	5	6.2:1
Present series	51	45	88	43	8	5.3:1
	161	128	79.5	139	22	6.3:1

3. *Seasonal Incidence.* The month of admission of each patient was tabulated. November and December have the highest incidence. Of the Friedländer pneumonias, 59% had their onset between November 1 and April 30. Solomon's²² comparable figure was 65%.

4. *Occupation.* This plays no rôle, and both whites and negroes are affected. Many of the patients have been debilitated; others have had preceding upper respiratory infections. Chronic alcoholism is probably a factor. Cold, exposure, malnutrition, foci of infection, trauma were all present occasionally but Friedländer pneumonia usually starts suddenly in previously healthy people.

EPIDEMIOLOGY. 1. *Incidence.* The reported incidence is low because of infrequent sputum cultures, and because the diagnosis is often not borne in mind. The proportion of Friedländer pneumonia among all pneumonias is reported variously as between 0.5% and 5%.^{5,6,13,20,22} The proportion is lower in large collected series of all pneumonias.

2. *Carriers.* The incidence of *B. friedländeri* in the normal upper respiratory tract varies greatly in different studies. Bloomfield⁵ found this bacillus in 5.8% of normal throats; Bullowa⁶ in 2.2% of 855 throats. Cooper found Friedländer bacilli in 1% of normal throats (Solomon²²) and Etienne, 4%. Harris²¹ in more than 500 throat cultures and mouse inoculations at Bellevue found Friedländer bacilli in less than 1% of patients without respiratory disease. The origin of the oft-quoted figure of a carrier rate of 25%¹² cannot be found, and it is difficult to accept this figure with the above findings.

Excepting Zander's large series,²⁷ which was without adequate bacteriologic study, outbreaks have been small. Kliewe, quoted by Bullowa, *et al.*⁶ reported an epidemic of infections of the upper respiratory tract and lungs due to *B. friedländeri* in 11 children who were exposed to a patient with known Friedländer pneumonia. Friedländer pneumonia is apparently less infectious than pneumococcal pneumonia.

Pathology. **MORPHOLOGIC.** 1. *Acute phase.* The following description is based on 13 autopsies of the 26 patients who died. When death occurred early (within the first 5 days), the pulmonary findings are characterized by the large, heavy, firm lobes, bright red color, and thick, gelatinous, tenacious, reddish-gray alveolar exudate.

Gross examination reveals the pneumonic lobes to be much heavier and larger than normally, non-crepitant, rubbery, firm, and consolidated. They are almost always bright red in color, much less often salmon or gray-colored. The pleura over the involved lobes is almost always roughened, dull, reddened, and covered with a heavy fibrinous exudate.

Section shows congestion, reddish-gray or brick red color, with a smooth (rarely dull) surface. Red and gray mottling is usually present. The alveolar exudate (also seen in the bronchi) is always thick, gummy, tenacious, glairy, mucoid, gelatinous, and reddish-gray or blood-tinged. In fewer than half of the cases, many small (1 to 6 mm.) abscesses with green-gray pus and friable débris can be seen.

Microscopically, the pleuræ are thick and congested, and covered with a heavy fibrinous deposit. There are often many neutrophils in this fibrinous layer. The alveoli are filled with serous or cellular exudate, which varies in quality in different areas of the involved lobes. The exudate may be serous, or may consist mainly of neutrophils, or mainly mononuclears, few large endothelial cells, and red blood cells. There is frequently a fibrinous meshwork in the more cellular areas. Many large clumps of bacilli may be seen within the phagocytes or free in the alveoli. The alveolar septa are destroyed in many areas and there are areas of intra-alveolar hemorrhages. The interlobar and intercinar septa are thickened and greatly enlarged. Postmortem cultures, shortly after death, yield Friedländer bacilli.

2. *Chronic Phase.* The main process is destruction of the parenchyma with abscess formation. One or more large cavities may be found. There is yellow pus, necrotic tissue, and coarse trabeculation of the abscess wall. Around the abscess is a pneumonitis of variable degree. Microscopically, there is cavitation, parenchymal destruction, much pus and débris without epithelialization of the cavity wall. Interlobular septa are thickened, and there is an infiltration of neutrophils and mononuclears around the abscess. The pleura is thickened and fibrotic.

OTHER FINDINGS AT AUTOPSY. Empyema, pericarditis, and meningitis each occurred twice. Of interest is the finding histologically, of portal cirrhosis in 4 patients (31%) and fatty liver in 5 patients (38%). One patient had both portal cirrhosis and extensive fatty infiltration of the liver. Spain²¹ found the incidence of portal cirrhosis to be about 6% of more than 3000 autopsies at Bellevue Hospital. Solomon²³ noted that "the association between cirrhosis of the liver and Friedländer infection is not uncommon."

Lobes Involved. Among the 51 patients, the right upper lobe of the lung was involved in 23 patients; the right middle lobe in 18; the right lower in 21; the left lower in 22; and the left upper in 19 patients. It can be seen that there is no preponderance of any one lobe.

TABLE 3—DATA OF 51 PATIENTS WITH FRIEDLÄNDER PNEUMONIA

Case	Age	Sex	Sputum character	Organism in sputum	Blood culture	Lobes involved	Associated diseases	Day therapy started	Day of death	Days of treatment	Case, treatment, clinical course, complications
1. G M.	67	M	Rusty	FBA	Pos (750 colonies)	RUL RML RLL	Arteriosclerosis	9	10	1	Sick 9 days before adm, ac fulminating course, aut FBA pneum, ac splenitis, cong of liver, myocard fibrosis
2 W M	60	M	Pink to red	FBA	Pos	LLL LUL RUL RML RLL	Portal cirrh, malnutrition, dehydration, arteriosclerosis	11	13	2	Ill at home 10 days, ac fulminating course, prontisol without effect, aut pneumonia of 5 lobes encaps empyema LUL, ac pericarditis
3 N K	58	M	Bloody red	FB	None	RUL RLL LUL LLL LUL	Portal cirrhosis, arteriosclerosis	None			Ac fulminating course, death in 4 hours, lung culture—FB, aut pneumonia portal cirrhosis, interstitial pancreatitis
4 R M	65	F	Dark, bloody, thick	FBA	None	LLL LUL	Diabetes mellitus	None			Grad downhill course of suppur pneumonia, repeated neg sputa for AFB, bronchoscopy neg, died at home after 3 months
5 A C	55	F	Thick, tenacious, bloody	FB	Neg	RUL RML RLL		None			Ac fulminating course, death within 24 hours
6 M P	56	M	Thick, brownish	FB	?	LLL		None			Ac fulminating, death in 20 hours
7 J S	61	M	Small amount, mucoid	FBA	None	RUL LLL	Pulm fibrosis	None			Grad improvement over 4 months, sputa repeated neg for AFB, lung puncture and duodenal bile revealed FBA
8 J McG	62	M	Copious, dark brown, prune-juice	FBA	Pos	RUL	Chr alcoholism	3	33	12	Ac ill, SP caused irreg response, foul, yellow sputum, Roentgen ray revealed large abscess, aut P M cultures of lung abscess, and bile pos for FBA, large abscess RUL, purul bronchitis, fatty liver
9 D O C	52	M	?	FBA	Pos	LLL RUL	Emphysema	None			Ac course death in 7 hours, coma with meningitis, FBA in CSF, aut P M cultures of lung meningitis, spleen pos for FBA, pneumonia, purulent meningitis

No.	J. I.	M.	Blood; small hemocytes, bloody; Ternaceous, bloody; Mucopurulent	FBA	Neg.	LUL LLL RUL RML RLL RUL	Sinusitis, pharyngitis Arteritis, heart disease; aur. fibrillation Syphilis	1	2	3	4	Ac. ill; ST and SD without response; RUL ab- sess cavity cleared markedly in 3 months; left fibrous scar; sputa neg. for AFB
10	J. L.	39	M	Bloody; small hemocytes, bloody; Ternaceous, bloody; Mucopurulent	FB	Neg.	LLL	1	1	..	3	Ac. ill; ST with good response; prompt resolution, Roentgen rays; sputa neg. for AFB
11	J. T.	40	M	Ternaceous, bloody; Mucopurulent	FB	Neg.	RUL	2	2	5	3	Dev. pneumonia on ward; acutely ill; good resp. to SP (not. temp. in 24 hours)
12	M. F.	67	M	None	FB (throat)	Neg.	RML	6	Elderly; comatose on adm.; incontinent; given ST and NaSP without resp.; died on 3d hospital day
13	N. H.	55	M	Yellow	FBA	Neg.	RUL	7	Subac. ill; ST and SD without response; RUL ab- sess cavity cleared markedly in 3 months; left fibrous scar; sputa neg. for AFB
14	E. O. C.	49	M	?	FBA	Pos.	LLL	8	8	18	7	Ac. ill at home, 7 days; temp. normal 24 hours after SP and NaSP; 4 days later rose to 104°; death
15	R. S.	52	M	Gelatinous; bloody- red mucoid	FBA	None	RUL	3	3	..	3	Afebrile in 48 hours after SD; good response; lungs cleared rapidly
16	J. M.	70	M	Small amount; mucoid	FBA	Neg.	RUL	8	Adm. stuporous; no history; ac. ill; moribund for 2 weeks; SD, no noticeable effect; temp. grad. fell to normal in 3 weeks Recovered.
17	L. G.	60	M	Thick, gelatinous, bloody	FB	None	LUL	None	None	Ac. ill; died on 5th day; aut.: Friedländer pneum.; sero-fibrin. pleurisy; fatty liver; coron. sclerosis
18	G. J.	51	M	Watery	FBA	Neg.	LLL	2	2	11	10	Ac. ill; no response to NaSP; icteric at death; aut.: lung and spleen cultures pos. for FBA; pneumonia; fatty liver; early portal cirrhosis
19	L. B.	58	M	?	FBA	Pos.	RML	2	2	..	21	Ac. ill; NaSD, 5 days without response; afebrile after 24 hours of NaSP; bile culture neg. for FB; grad. improved; small rt. encaps. pleural effusion.
20	C. R.	72	F	Scant, mucoid	FBA	Neg.	RUL	1	1	..	7	Ac. ill; afebrile 24 hours after SP started; chest cleared rapidly
21	E. S.	49	M	Blood-tinged; mucopurulent	FB	?	LLL	None	None	Subac. course with abscess; sm. spontan. pneumo- thorax over LUL, which cleared; sputa repeatedly neg. for AFB and pneumococci; grad. recovery
22	P. K.	63	M	Thick, bloody; non-foul	FB	None	LLL	62	10	Subac. ill, 2 weeks before adm.; ST no effect; became afebrile 24 hours after SP, but became toxic, weaker, and went downhill; sputa neg. for AFB
23	E. M.	47	F	Thick, yellow	FBA	Neg.	LUL	Had empyema and chest wall abscess; FBA from both; thoracotomy and SP; grad. improved; thor- acotomy fistula healed; sputa neg. for AFB
24	A. G.	50	M	Scanty, salmon-col- ored	FBA	Pos.	RUL	6	6	..	21	Acu. ill; SF and protylin without temp. response, but grad. improved; residual RUL cavity; LLL pneumococcal type I pneumonia with bacteremia in 1940 with good response to SP; No FB or AFB in sputum.

For key to abbreviations, see footnote, page 667.

TABLE 3—DATA OF 51 PATIENTS WITH FRIEDLÄNDER PNEUMONIA—(Continued)

Case	Age	Sex	Sputum character	Organism in sputum	Blood culture	Lobes involved	Associated diseases	Day therapy started	Day of death	Days of treatment	Onset, treatment, clinical course, complications
25 A B	59	F	Thick tenacious, bloody, rusty	IB	Neg	LUL, LLL, RML	Bronchial asthma	2		21	Ac ill given SD and ST, no marked effect grad improved after 2 weeks
26 A L	47	M	Thick, bloody	IB	Pos	RML, LLL, RUL	Morphine addiction, malnutrition	None			Chr and ac ill died shortly after adm, aut I redl under pneum, massive gangrene and multiple abscesses of lung, early portal cirrhosis
27 L M	65	M	Mucopurulent, brown	IB	Pos	RML, RUL, RLL	Diabetes mellitus	None			Ac ill, constose, neck rigidity IB in C-1, meningitis Died
28 P O D	71	M	Scanty mucoid	IB	?	RUL, LUL, LLL	Chr alcoholism, portal cirrhosis	None			Ac ill, died on 3d day, liver palpable
29 P L	18	M	Thick, bloody	IB	Neg	RUL, LUL, LLL	Chr alcoholism, portal cirrhosis	None		9	Ac fulmin course, death in 21 hours
30 J T	12	M	Thick, bloody, tenacious	IBB	Pos	RUL, LUL, LLL	Chr alcoholism, portal cirrhosis	None			Ac ill, semicomatose, died on 3d day, aut I redl under pneum, left empty pur pericard portal cirrhosis
31 J H	56	M	Dark brown	IBB	None	RLL	Chronic alcoholism	7			Ac ill, after SD temp fell from 103° to 101° in 21 hrs, grad recovery
32 J K	40	M	Dark bloody hemoptysis	IBA	Neg	RLL	Chr alcoholism, fatty liver	None			Ac fulmin course, died in 24 hours
33 B W	45	M	Thick, bloody, gelatinous, homogeneous	IB	Pos	RUL, RML, RLL	Chr alcoholism, fatty liver	None			Ac ill died in several hours after admission
34 C L	50	M	Mucoid red, thick	IB	Pos	RUL, RML, RLL	Chr alcoholism, fatty liver	None			Ac ill anti-pneumococcus type II serum without effect, died, 3d hospital day, aut I redl under pneum, fatty liver
35 J M	59	M	Mucoid red, thick	IBB	Pos	RUL, RML, RLL	Chr alcoholism, fatty liver	None			Ac fulminating course, pre-terminal death in 6 hours, IB in lung suction
36 J McG	69	M	Loose	IB	Pos	RUL, RML, RLL	Chr alcoholism, fatty liver	2			Developed pneum in hosp, temp fell to 100° 21 hours after SD, grad recovery
37 A M	48	M	Bloody am hemoptysis	IB	Pos	RUL, RML, RLL	Cerebral thrombosis	None			Ac fulminating course, liver down to umbilicus death in 18 hours, aut P M lung culture gave IB I redl under pneum early abscesses

39. B. B.	67	M	Small hemoptysis	FBA	Neg.	LLL	Prostatic hypertrophy	7	..	5	11 week before adm.; given SP with good response; had FBA in urine for 2 years since pneumonia; no FB in sputum after pneumonia
39. J. M.	41	M	Thick, rusty, blood-streaked	FBB	Pos.	RUL RML	Chr. alcoholism, portal cirrhosis	1	80	11	Ac. ill; fair temp. response to SP, but went grad. downhill; telerus and ascites with FBB in asc. fluid
40. M. C.	50	M	Thick, rusty, blood-streaked	FBA	Neg.	RUL RML	Chr. alcoholism, fatty liver	7	..	10	Ac. ill; small hemoptyses and pleurisy; given SP without response; abscess of RUL yielded FBA
41. G. B.	58	M	Small hemoptysis	FBB	Neg.	LLL LUL	Diabetes mellitus, portal cirrhosis	1	..	9	Developed pneum. on ward, after early neg. chest Roentgen ray; ac. ill; treated with SP, NaSP and 50 cc. anti-FB serum; grad. recovery over 2 months
42. A. P.	53	M	Thick, blood-streaked	FB	Pos.	RUL RML	Chr. alcoholism, portal cirrhosis	14	..	9	Described in text
43. J. A.	53	M	Thick, bloody; tenacious	FBA	Neg.	LUL LLL	6	..	7	Described in text
44. E. K.	50	F	Thick, rusty; tenacious	FBA	Neg.	RML LLL	Portal cirrhosis	Ac. ill; pneum. spread while receiving SP; devel. ieterus and ascites; mult. lung abscesses drained; pneum. slowly resolved with fibrosis in 4 months
45. G. B.	57	M	Bloody; thick; tenacious	FBB	Pos.	RUL RML	Chronic alcoholism	4	..	9	Described in text
46. M. C.	67	M	Scant; mucoid	FBB	Pos.	RUL	Chronic alcoholism	1	..	60	Ac. ill; temp. fell grad. over 6 weeks; mult. cavities of RUL; pt. in hosp. now; FBB in sput. for 2 months
47. R. G.	43	M	Sm. hemoptysis	FB	Neg.	LUL	None	Devel. LUL abscess; grad. clearing and fibrosis over 6 months; sputa neg. for AFB
48. J. M.	51	F	Thick, yellow; blood-streaked	FB	Neg.	LUL	Diabetes mellitus	None	Ac. ill; LUL abscess with fluid; grad. clearing over 4 months with fibrous scar
49. B. D.	40	F	None	...	Pos.	RML RLL	Chronic alcoholism, malnutrition	None	Ac. ill; died, 7 hours; aut.: Friedländer pneum.; fibrin. pleurisy; fatty liver; P.M. cult. of heart, blood, lung pos. for FB
50. I. R.	37	M	Tenacious; mucopurulent with blood-streaking	FB	Pos.	LUL LLL	None	Ac. ill, dying in 4 days (before chemotherapy available); aut.: pneum., pur. meningo-encephalitis; P.M. cult. of ht., blood, lung, spleen, pos. for FB
51. J. D.	23	M	Thick, rusty, bloody	FB	Neg.	RLL	None	Ac. ill; grad. clearing of pneum. over 6 weeks; sput. neg. for AFB; follow-up 2 years later revealed nor. chest Roentgen ray, nor. bronchograms of RML and RLL

Abbreviations: FB, Friedländer bacillus; type A, etc.; AFB, acid-fast bacilli; SF, sulfanilamide; SP, sulfapyridine; ST, sulfathiazole; SD, sulfadiazine; NaSP, sodium sulfapyridine. Lobes: RUL, right upper lobe; LLL, left lower lobe; LUL, left upper lobe, etc. M, male; F, female; adm., admission; P.M., postmortem; CSF, cerebrospinal fluid. Cases 23, 24, 39, 40, and 43 correspond to Cases 14, 16, 13, 12, and 15 of Solomon's report.²³ They are re-presented because of the interesting follow-up observations. Cases 47 through 51 were observed at the New York Hospital.

Bronchoscopic Findings. Seven patients were examined by bronchoscopy during the subacute or chronic phase of their illness. One examination was negative, while the remaining 6 revealed mucus coming from the bronchi of the affected lobes. The bronchial mucosa was noted to be injected in the affected branches.

Clinical Course. Onset. As noted by previous observers, the onset of Friedländer pneumonia, like pneumococcal lobar pneumonia, is usually sudden with cough (91% of cases), sputum (90%), chest pain (82%), and chill (58%). Occasionally prodromata of "colds," upper respiratory infections, and cough were present. Rarely vomiting and epigastric pain were the first symptoms. The patient always appeared acutely ill and dyspneic; often cyanotic and febrile. The admission diagnosis was usually "lobar pneumonia."

Temperature. The first day temperature was below 102° F. in 13 patients (26%); between 102.2° and 104° F. in 31 patients (62%); and 104.2° F. or above in 6 cases (12%). Pulse rates always corresponded to the temperature curve. Previous observers have noted that the temperature does not commonly rise above 102° F. This was noted in 50% of Solomon's cases.²² In the present series, however, 74% of all patients had first day temperatures of 102.2° F. or above, simulating other types of lobar pneumonia. Perlman and Bullova²⁰ found that the temperature, pulse, and respiration curves did not differ significantly from those of pneumococcal lobar pneumonia.

Leukocyte Counts. On admission these were tabulated in 4 groups:

Leukocytes	Patients	%
less than 5,000	3	6
5,000 to 11,000	11	24
11,000 to 20,000	20	43
20,000 and above	13	27

Thus it is to be observed, in a patient acutely ill with pneumonia, a normal leukocyte count may be of slight help in arousing suspicion of Friedländer pneumonia. The same phenomenon is often observed in virus pneumonia, and in the aged.

Physical Signs. The physical signs were varied and indistinguishable from those of pneumococcal lobar pneumonia.

Roentgenogram. Kornblum and Collins^{18,9} have observed 4 stages, based on serial chest films: (1) primary bronchopneumonia, (2) secondary pseudolobar confluence, (3) necrosis with formation of multiple thin-walled abscess cavities, and (4) the stage of fibrosis and healing. The resemblance of the stage of multiple thin-walled or large abscess cavity to pulmonary tuberculosis has been noted by many observers. During the acute Friedländer pneumonia, the "predominant finding is a massive, dense, usually homogeneous shadow, which was frequently suggestive of fluid."⁶ The sequence noted by Kornblum, Collins and others occur in about one-third of the patients (the group entering the chronic phase). Most patients, including those who die, reveal only the dense massive shadow of

consolidation and a few pass from consolidation to resolution, without pulmonary necrosis and abscess formation.

Sputum. The sputum on admission was almost always described as "thick," "bloody," "tenacious," "gelatinous," "small hemoptysis" (see Table 3).

Bacteremia. The bacteremia is usually slight quantitatively. Previous observers have noted the lack of relationship of mortality to bacteremia, but in the present series, the mortality rate of non-bacteremic cases (23%) is lower than that of bacteremic patients (82%).

Table 4 is a compilation of several large reported series of Friedländer pneumonia, including the present.

TABLE 4.—BACTEREMIA AND MORTALITY RATE

	Solomon 1937	Bullowa 1937	Bullowa 1941	Present series	Present series	
					acute only	chronic only
Total no: of cases	32	41	37	51	36	15
Deaths	31	34	31	26	23	3
Mortality rate	97%	83%	84%	51%	64%	20%
No. of cases with blood cult.	27	41	37	40	27	13
No. of bacteremic cases	19	27	12	18	14	4
Per cent of bacteremic cases	70%	66%	32%	45%	52%	31%
No. of fatal bacteremic cases	19	25	9	14	12	2
Mortality rates of bacteremic pts.	100%	92%	75%	82%	85%	50%
No. of cases without bacteremia	8	14	25	22	13	9
No. of fatal cases without bacteremia	7	7	22	5	5	0
Mortality rate of non-bacteremic cases	87%	50%	88%	23%	40%	-

Course. Acute primary Friedländer pneumonia may lead to early death (one-half of our cases), fairly prompt recovery with resolution of the pulmonary lesion (in about one-sixth of our cases); or parenchymal destruction with necrosis and abscess formation (the chronic phase, which occurred in about one-third of our cases). Table 3 outlines the course of each patient.

Complications. Among this group of 51 patients, at least 15 had clinical evidence of lung abscess. At necropsy, most had parenchymal destruction of variable degree. Meningitis proven by positive cerebrospinal fluid cultures for Friedländer bacilli was found in 2 patients; purulent pericarditis twice; and a small apical spontaneous pneumothorax on the affected side twice. Pleural fluid was present clinically in 8 patients, the fluid being encapsulated and purulent with positive *B. friedländer* cultures in 3 of these. The remaining 5 effusions were clear, serous, and sterile.

A complication not reported previously is the subsequent development of pulmonary tuberculosis. Amberson has repeatedly emphasized the adverse effects of suppurative disease on old and inactive pulmonary tuberculosis. Baum and Amberson³ have recently reported a series of patients stressing this again. Three of the present group of 51 patients have developed pulmonary tuberculosis.

Case Reports. CASE 43. One patient (J.A.) was included in Solomon's 1940 report as Case 15. He was admitted on June 10, 1939 with a Friedländer type A pneumonia and developed a lung abscess and encapsulated

empyema. Thoracotomy was performed on July 7; subsequently a bronchopleural fistula developed. Cultures of the abscess and empyema pus showed Friedländer bacillus, type A. Recovery was slow, but the patient was able to return home on January 16, 1940, with his patent bronchopleural fistula. Repeated sputa on this admission were negative for acid-fast bacilli. On July 10, 1941, there was a small hemorrhage from the chest wall sinus. He was immediately hospitalized. Two days later, he had a small hemoptysis. Sputa thereafter were repeatedly positive for acid-fast bacilli. Chest films revealed bilateral infiltrations. The old thoracotomy and abscess precluded accurate visualization of the left lung. The patient was transferred to a tuberculosis sanatorium. Follow-up (March, 1942) reveals a persistent left thoracotomy wound with moderate drainage from the residual empyema cavity. On the right, there is a tuberculous cavity, 3 cm. in diameter. Sputum and pus from the left thoracotomy are both positive for acid-fast bacilli. There are no Friedländer bacilli in the sputum at present.

CASE 42. A.P., a 53-year-old white male, was ill about 2 weeks before admission on October 8, 1940. His sputum was thick and blood-streaked. Sputum and blood culture yielded Friedländer bacilli. A type XXI pneumococcus was also present in the sputum. He was treated with sulfapyridine and 240,000 units of type XXI anti-pneumococcal serum (rabbit) with no apparent effect. A Francis skin test with SSS of pneumococcus type XXI was negative. Sputum concentrates were negative for acid-fast bacilli at this time. A small right pleural effusion was noted on October 15. This fluid was clear and negative for pyogenic and acid-fast organisms on culture and smear. On November 6, he developed a bronchopleural fistula with empyema. Empyema fluid was positive for acid-fast bacilli. He was transferred to a tuberculosis sanatorium where a thoracotomy was done later. When last seen (March, 1941) he had a bronchocutaneous fistula, mixed tuberculous empyema, and his sputum was positive for acid-fast bacilli.

CASE 45. G.B. is still a patient in the hospital. He was admitted on September 9, 1941, after having been ill at home for 4 days. His sputum was mucoid, non-foul, and bloody; two blood cultures yielded Friedländer bacilli, type B. He was treated with sulfathiazole, without any apparent response. On September 17, he was given 200,000 units of anti-pneumococcal type 2 rabbit serum, intravenously, and this was repeated on the following day, without any noticeable effect. The patient was kept in bed. His first 5 sputa concentrates were negative for acid-fast bacilli, but positive sputa were secured on October 21 and 23. Since then, however, repeated sputa concentrates have been negative for acid-fast bacilli. A urine culture yielded Friedländer bacillus, type B, but was negative for acid-fast bacilli. It is believed that small tubercles have been eroded. This patient is being closely observed to see whether clinical pulmonary tuberculosis will develop.

Serial chest films and repeated examination of the concentrated sputum for acid-test bacilli are most important. Prolonged bed rest is indicated.

Diagnosis. The type-picture of Friedländer pneumonia is an acutely ill male over 40 years of age, with a history of sudden onset of cough, chest pain, and chill, with thick bloody sputum or a small hemoptysis, with an initial temperature above 102.2° F., and signs of lobar consolidation. The diagnosis should be considered in all adult cases of pneumonia of unclear etiology. Sputum and blood cultures should always be secured immediately; these may show the characteristic growth in 24 to 48 hours. A Gram stain will reveal the large, Gram-negative bacilli with heavy capsule. Intraperitoneal injection of the sputum into a mouse will cause death within 24

hours, with many Gram-negative encapsulated bacilli in the peritoneal exudate and heart's blood.

Mortality. The mortality rate of the present series is 51%. The mortality rate does not vary significantly with the age of the patient. Disregarding any therapy received, the mortality rate of this group of patients prior to 1939 was 75%; since then, 35%. The mortality rate varied with the number of lobes involved. Thus, it was 26% with unilobar pneumonia; 65% if two or more lobes were involved. There was no significant relationship of the mortality rate to the admission white blood count.

Of the present series, 29 sputa were typed and of these 79% were type A. Julianelle,¹⁶ in a carefully studied group, found that type A was the etiologic agent in 74% of 45 cases of Friedländer pneumonia, and type B in 4% of these cases. Cooper found Friedländer bacillus, type A, in 95% of her cases, and Solomon²² in the 10 cases whose sputa were typed, found type A in all. Bullowa⁶ found type A in 73% of 33 cases in 1937, and in 79% of 37 cases in 1914. There is no significant variation of the mortality rate for types A and B. Table 5 indicates the relationship of type of organism to the sex of the patient. Of 73 typed sputa, the male to female incidence of type A Friedländer pneumonia is almost 10:1; for type B, it is 3:1.

Of those patients who died, 45% did so within 4 hours of admission to the hospital (usually on the 3d to 6th day of illness) and 80% of all deaths occurred within 5 days of hospitalization. The correlation of mortality rate and bacteremia has been discussed above (Table 4). One patient, not included in this series, had both Friedländer bacilli and pneumococcus type XVIII in sputum and blood cultures. Both organisms were recovered in the mouse. The patient died shortly after admission. This is evidently a case of true mixed infection.

Treatment. *Experimental.* Buttle *et al.*⁷ showed that sulfanilamide had little effect in treating mice infected with Friedländer bacillus. Bliss *et al.*⁴ found that sulfapyridine was slightly more effective than sulfanilamide in prolonging survival of mice infected with Friedländer bacillus, type B. This was also noted by Kolmer and Rule.¹⁷ Feinstone *et al.*,¹⁰ using mice and a strain E of type B Friedländer bacillus, found that sulfanilamide, sulfapyridine, and sulfathiazole revealed practically no demonstrable therapeutic effect. Sulfadiazine, however, had a markedly beneficial effect. Thus, with the same dose of each drug, these workers found a survival rate of 6% for sulfapyridine and 73% for the sulfadiazine-treated mice. Table 6 is an abbreviation of one of their tables.

It must be emphasized that these data are derived from laboratory studies on mice, using a single strain of Friedländer bacillus, type B. Clinical experience does not substantiate this marked therapeutic advantage of sulfadiazine over other sulfonamides in human Friedländer pneumonia. The varied responses to chemotherapy may be explained by the presence of different strains of Friedländer bacilli.

Clinical. The evaluation of therapy in Friedländer pneumonia is very difficult. Solomon²² reported a mortality rate of 97% among 32 acute cases without chemotherapy. Five of his 32 cases received type A, anti-Friedländer horse serum, but in small amounts; all died. Bullowa, Chess and Friedman⁶ had 6 patients who were treated with *B. friedländeri*, type A serum, with 3 recoveries. These 3 patients had negative blood cultures. Of 18 of their patients with Friedländer pneumonia, type A, without any serum therapy, 17 (94%) died; 10 of these had bacteremia. Perlman and Bullowa²⁰ found sulfanilamide, sulfapyridine, or serum, or combinations of these were of little value. In evaluating mortality tables, patients living long enough to receive therapy and those in whom therapy was of value in prolonging life must be differentiated. One is impressed in reviewing the protocols (Table 3) by the frequent fall of temperature to 99° F. or to normal within 24 to 48 hours after institution of sulfapyridine therapy. Of importance is the time chemotherapy is instituted. In those patients where the day of onset of symptoms and therapy was clear, the mortality rate was 13% when therapy was begun on the 1st day of the pneumonia, and 50% when chemotherapy was begun later. The value of chemotherapy is not clear. However, sulfonamides appear to have some value in human Friedländer pneumonia in the early stages. They probably have little value after suppuration occurs. Further trial of the sulfonamides is clearly indicated.

TABLE 5.—RELATIONSHIP OF TYPE OF FRIEDLÄNDER BACILLUS TO THE SEX OF THE PATIENT

			Bullowa, <i>et al.</i> 1937	Perlman and Bullowa, 1941	Present series	Totals
Type A.	M	22	28	19	69
	F	2	1	4	7
Type B.	M	2	4	6	12
	F	0	4	0	4
Untyped.	M	12	—	18	
	F	3	—	4	

TABLE 6.—MICE SURVIVAL AND CHEMOTHERAPY.

(Adapted from Feinstone, Williams, Wolff, Huntingdon, and Crossley.¹⁰)

	No. of mice	Mice surviving	% survival
Sulfanilamide	100	2	2.0
Sulfapyridine	99	6	6.0
Sulfathiazole	100	2	2.0
Sulfadiazine	86	63	73.6
Controls	78	0	0.0

After the patient enters the chronic phase, therapy is conservative. Most patients do well and these lesions go on to complete healing, often with fibrous scars. Patients with chronic lung abscess require a prolonged period of bed rest with serial chest films. The abscesses are non-putrid and do not contain anaërobcs, which may explain the tendency to heal. If healing does not occur, the question of thoracotomy arises. None of the present series of patients underwent surgical intervention during the chronic phase. Two

patients (Cases 23 and 44) had thoracotomies with drainage of the acute Friedländer lung abscess. Both did well and went on to healing. The ideal management of the non-healing residual abscess cavity is not clear, as there have been too few cases.

Follow-up observations on 10 patients now living, at varying intervals after their attacks of Friedländer pneumonia, reveal:

CASE 13. N.H., 3 months after onset of his pneumonia, still has residual infiltration, parenchymal destruction, and fibrosis but serial films have revealed progressive clearing. Sputum negative for acid-fast bacilli.

CASE 19. L.B., 10 months after onset of Friedländer pneumonia is feeling fine and has no complaints. Physical and roentgenographic examinations of the chest are negative.

CASE 23. E. M., 2½ years later, still has persistent cough with about 300 cc. mucopurulent sputum. Examination of chest reveals many coarse moist rales with bronchovesicular and bronchial breath sounds over the entire left lung, anteriorly and posteriorly. Bronchograms in May, 1942 reveal bronchiectasis of left upper and lower lobes. Friedländer bacilli, type A, are still present in her sputum. This patient may have had previous bronchiectasis.

CASE 24. A. G., 2½ years later has a residual cavity, but feels fine. Sputum negative for acid-fast bacilli and Friedländer bacilli. No cough.

CASE 25. A. B., 1 year later feels fine and has no complaints. Physical examination of chest and chest roentgenogram are both negative. Throat culture revealed no Friedländer bacilli.

CASE 31. J. H., 3 months later has occasional cough without sputum. He has gained 10 pounds. Examination of chest and chest roentgenogram are both clear. Throat culture is negative for Friedländer bacilli.

CASE 36. J. McG. is in a hospital for chronic disease because of his hemiplegia. Friedländer bacilli were present in the sputum for 18 months after his acute pneumonia, but are now absent.

CASE 38. B. B., 2 years later feels well. Chest examination and chest film are negative. Urine culture still reveals Friedländer bacilli, type A. Throat swab is negative for Friedländer bacilli.

CASE 40. M. C., 3 years later has a chronic cough with occasional blood-streaking. Weight has been stationary. Physical examination of the chest was negative. Chest film revealed thickened, fibrotic interlobar fissure between the right upper and middle lobes. Sputum is negative for Friedländer bacilli.

CASE 41. G. B., 2 years later has no complaints. Chest examination and roentgenogram are negative. Sputum culture reveals no Friedländer bacilli.

Summary and Conclusions. 1. Based on the present series of 51 patients with Friedländer pneumonia, 88% of the cases were more than 40 years of age. The ratio of males to females was more than 5 to 1. Almost 60% of all cases occurred in the 5-month period from November 1 to April 30. Occupation played no rôle.

2. The apparent incidence of Friedländer pneumonia at Bellevue Hospital is 1.6% of all pneumonia. The actual incidence is probably higher. The incidence of carriers of *B. friedländeri* is 1% or less, based on recent surveys. Several carriers of *B. friedländeri* have been found to have bronchiectasis. Friedländer pneumonia is less infectious than pneumococcal pneumonia.

3. The morphologic findings at necropsy of the acute Friedländer pneumonic lung have been described.

4. The incidence of fatty degeneration of the liver and portal cirrhosis at necropsy may be higher in patients with Friedländer pneumonia than in the general population. Larger series of cases will be necessary to decide this.

5. All lobes were about equally involved with pneumonia. Bronchoscopies during the chronic phase usually revealed mucopus coming from the bronchi of the affected lobes.

6. The onset of Friedländer pneumonia is sudden with cough (91%), sputum (90%), chest pain (82%), and chill (58%). The patient is usually acutely ill and dyspneic; often cyanotic and febrile. First day temperature of 102.2° F. or above was present in 74% of patients. The admission sputum was described as "thick," "bloody," "gelatinous," or "small hemoptysis."

7. Bacteremia is usually slight quantitatively. Positive blood cultures were present in 45%. The mortality rate for bacteremic patients was 82%; for non-bacteremic patients, 23%.

8. The roentgenogram of the chest usually revealed a dense, homogeneous shadow of consolidation. This was followed by death, or complete resolution within a short period, or pulmonary necrosis which usually went on to fibrosis and healing.

9. Among the complications were meningitis, purulent pericarditis, and small apical spontaneous pneumothorax, each occurring twice (4%). Pleural effusion was present in 8 patients (17%), the fluid being purulent in 3 of these. Pulmonary tuberculosis later developed in 3 patients (of 15 who entered the chronic phase). Serial chest films and repeated examination of sputa concentrates for acid-fast bacilli are most important.

10. Diagnosis is simple if Friedländer pneumonia is borne in mind. Routine cultures of the sputum as well as the blood of all patients with pneumonia is indicated.

11. The gross mortality rate of the present series is 51%. There is no significant variation of the mortality rate for types A and B. Of all deaths, 80% occurred within 5 days of hospitalization.

12. Although some experimental data on mice favor sulfadiazine, a review of the protocols of the present series indicates that sulfa-pyridine may be the drug of choice in acute Friedländer pneumonia. However, at best, chemotherapy has proved to be only of questionable value in most cases, and a final decision must be withheld at this time. In the chronic phase, the management is conservative and usually non-surgical, as most of these lesions will go to fibrosis and healing.

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INCIDENCE OF BRONCHIAL ASTHMA IN THE WHITE AND NEGRO

BY VINCENT J. DERBES, M.D.

AND

HUGO T. ENGELHARDT, M.D.

NEW ORLEANS, LA.

(From the Department of Medicine, School of Medicine, Tulane University of Louisiana)

CONSIDERABLE confusion exists with regard to the relative racial incidence of various diseases although there is a slowly growing literature on the subject. One of the earliest and most comprehensive monographs is that of Matas⁸ which consists of a general survey, surgical in nature, of disease incidence in whites and negroes. Since this time a number of articles dealing with some particular phase of the subject have appeared.^{2,5,6} A rather thorough inquiry into

the literature has failed to reveal any articles dealing with the incidence of asthma in the negro though Scheppegegrell⁹ emphasized that colored people were afflicted with hay fever about one-third as often as whites. Indeed it seems to be the general impression that negroes are relatively immune to allergic diseases. It is of passing interest that Hrdlicka,⁷ who had extensive experience with American Indians stated that asthma is rare among Southwestern Indians and that no instance of severe asthma was encountered; Coca³ questioned physicians dealing with Indians whose replies suggested that while the allergic trait is not absent in the Indian race it is very much less marked in the Indian than the white.

Using the data compiled from army experience in the World War I, Davenport and Love⁴ classified their cases into total admissions from bronchial asthma; ratio of admissions per thousand; length of hospital stay and mortality rate (see Table 1). Inasmuch as there were many fewer negro than white troops the total values are correspondingly smaller for the former; the relative values are higher however, in every respect. Thus in this selected group of so-called normal males of military age, there was more asthma in negroes than in whites and it was apparently of severer grade as concerned both morbidity and mortality.

TABLE 1.—INCIDENCE OF BRONCHIAL ASTHMA IN WHITES AND NEGROES
(Army Data From World War I)

	White		Negro	
	Total	Ratio/1000	Total	Ratio/1000
Admissions	6,453	1.79	1,017	3.55
Days lost	157,818	.12	20,118	.19
Discharges for disability	2,433	.68	439	1.53
Deaths	24	.01	10	.03

We have been impressed in dealing with large numbers of negro patients at Charity Hospital that bronchial asthma is certainly not rare in the negro. In order to determine whether this clinical impression was correct we turned to the data derived from cases seen at the Charity Hospital of New Orleans over a 5-year period from 1937 through 1942.

Reference to Table 2 will show that in our series asthma is approximately half again as common in the white as in the negro.

TABLE 2.—INCIDENCE OF BRONCHIAL ASTHMA IN WHITES AND NEGROES
(Charity Hospital Cases From July 1, 1937 through June 30, 1942)

	White		Negro	
	Male	Female	Male	Female
Admissions by race and sex	71,393	79,647	59,212	85,272
Number of cases	496	509	239	324
Ratio of admiss. per 1000 . .	6.95	6.39	4.04	3.79
Hospital stay (in days) . . .	9.03	8.34	9.13	8.26
Deaths	38	10	8	8
% deaths	7.66	1.96	3.35	2.47

We were, however, impressed with the fact that the hospital stay was essentially the same in the two races. Our data are paralleled by the findings of Adams¹ who studied a large group of white and colored

workmen. He found that in the respiratory group of diseases the frequency for whites is greater, but that the duration per case is, however, greater for the colored resulting in more time lost per individual by the colored than by the white. He noticed this racial difference in all cases of respiratory diseases. Perhaps this discrepancy is to be explained by the findings of Smillie and Augustine¹⁰ who in a careful study of the vital capacity of the negro race observed that the vital capacity in both sexes and for all age groups studied is markedly lower than the vital capacity of the white race. When calculated from surface area, the difference is 15% to 20% in children and 25% to 35% in adults.

Although it is a clinical impression that few people die of bronchial asthma; and indeed this is borne out by the army experience, there was a number of deaths recorded in our series.

From the army experience, as well as our own, it is concluded that bronchial asthma is a common disease among negroes.

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BLOOD STUDIES IN THE AGED

THE ERYTHROCYTE IN THE AGED MALE AND FEMALE

BY BERNARD NEWMAN, B.S., CH.E.,

AND

SAMUEL GITLOW, M.D.

NEW YORK, N. Y.

(From the Hospital and Home of the Daughters of Jacob)

In a previous paper from this institution,¹⁸ it was shown that the ascorbic acid state of the aged individual was far from the ideal. In 1930, Mettier, Minot, and Townsend¹¹ showed that an anemia resulted from a deficiency of vitamin C. These observers further noted that when scorbutic patients showed an anemia, iron and liver therapy produced little or no effect on blood formation; but with an addition of vitamin C to the diet, marked response was obtained. In view of these findings, it was thought of interest to investigate the hematology of the normal aged individual. It was considered of further interest to compare our findings with the "normal" values reported in the literature.

Experimental Procedure. The subjects used in this study comprised 50 males and 50 females. They were all ambulatory, and were housed in the "Home" division of the institution. They gave no clinical evidence of disease, and beyond a slight degree of myofibrosis, were electrocardiographically negative. No individual who gave either clinical or electrocardiographical evidence of coronary disease was used. The usual dietetic regimen was adhered to, and during the 48-hour period preceding this study, they received no medications. The ages of the males ranged from 65 to 91 years, with the average age being 78.3 years, and the ages of the females were from 66 to 104 years, with the mean age at 77.2 years.

Venous blood was withdrawn from the fasting subject by means of a 20-gauge needle. As soon as the needle entered the vein, the tourniquet was removed, and a period of at least 2 minutes was allowed for restoration of normal conditions before removing the blood. Two cc. of blood was removed in each case.

As an anticoagulant, a mixture of 4 parts of ammonium oxalate and 6 parts of potassium oxalate was used, since this mixture does not cause any shrinkage of the blood cells.¹⁹

Hemoglobin determinations were made in duplicate, using a Sahli type hemoglobinometer, with a 15-minute period being allowed after the addition of the blood to the hydrochloric acid, before reading the results. Weekly determinations, in duplicate, of the blood iron using the method of Wong²⁰ were made, as a means of checking the hemoglobin.*

Red blood cell counts were made in duplicate, using 2 different pipettes certified by the U. S. Bureau of Standards, on a certified Spencer "Bright-line" hemocytometer. Hayem's solution was used as the diluting fluid.

The volume of packed cells was determined by placing the well-mixed blood in a Sahli hemoglobinometer tube to the 100 mark, and centrifuging at high speed until the maximum packing of the cells took place.²¹ The volume of packing was then noted. The percentage relative to the "normal" was calculated by dividing this determined value by the "normal" value of the packed cells, in this case assumed to be at 48.0 cc. for the males,²² and 46.0 cc. for the females.²³

The resistance of the red cells to hypotonic salt solutions was determined as follows: Reagent grade sodium chloride was heated over a flame until all the adsorbed moisture was driven off. It was then kept in a desiccator over anhydrous calcium chloride until needed. Exactly 1.0000 gm. was weighed out on an analytical balance, dissolved in distilled water, and made up to 100.0 ml. in a volumetric flask in a water-bath at 20° C. A series of dilutions of saline was next prepared, ranging from 0.5% to 0.2%, in steps of 0.02%. Two cc. of each dilution was placed into each of a set of test tubes properly labeled as to the salt concentration, and a drop of the blood to be tested added to each. At the same time, another set of tubes was prepared as previously, and a drop of blood from a young healthy adult was added to each. Both sets of tubes were well shaken and set aside at room temperature for 2 hours, at the end of which time, the tube in which hemolysis began, and that in which hemolysis was complete was noted. (If the normal blood varied by more than 0.04% from the accepted normal figures of 0.44% for minimal resistance and 0.32% for complete hemolysis²⁰ the test was repeated using fresh dilutions of saline.)

Reticulocyte counts were done by making blood smears on slides that had been prepared in advance by having a thin film of cresyl blue on them, and counterstaining with diluted Wright's stain.¹⁶ A total of 500 red cells was counted and the percentage showing reticulum noted.

* Where normal values for hemoglobin have been determined by the oxygen-combining capacity of the blood, an assumption is made, namely, that the oxygen-combining power of the blood is 1.34 cc., i. e., 1 gm. of hemoglobin will combine with 1.34 cc. of oxygen at standard conditions. However, this figure has never been determined with certainty, and the value, 1.34, is at best only an approximation.²⁴ On the other hand, the iron content of the hemoglobin molecule is accurately known.²⁵ Hence, an analysis of the cells for the iron content gives an extremely accurate method of indirectly measuring the hemoglobin.

With the above technique, hemoglobin values were found ranging from 9.7 gm. per 100 cc. to 15 gm. per 100 cc. for the males, and from 9.5 gm. per 100 cc. to 16 gm. per 100 cc. for the females. The mean hemoglobin concentration for the male group was found to be 12.65 gm. per 100 cc., while the mean value for the females was 11.7 gm. per 100 cc. In computing the percentage hemoglobin, the value 14.5 gm. was used as representing 100% for both sexes.¹⁸ Table 1 shows the distribution of the hemoglobin values for the males, and Table 2 shows the corresponding values for the females. Table 3 presents the absolute and the percentage hemoglobin of the various age groups for both males and females.

The results of red blood cell counts may be found in Tables 1 and 2. Table 3 shows the mean erythrocyte counts for each age group for both sexes, the values ranging from 3.30 millions per c.mm. to 5.09 millions per c.mm. for the males, and from 3.2 millions to 5.21 millions per c.mm. for the females, the average male and female values being 4.42 millions per c.mm. and 4.11 millions per c.mm., respectively.

Volumes of packed cells were obtained ranging from 35 to 52.2 cc. per 100 cc. for males with an average volume of 41.2 cc., and for the females, 26 cc. to 52 cc. per 100 cc., with an average of 36.7 cc. These figures correspond to a percentage of 72.9 to 109 of the "normal," with the average mean value being 85.8%, and from 54 to 113%, with an average of 80% for males and females respectively. The results of these determinations may be found in Tables 1 and 2. The mean values for the various age groups are seen in Table 3.

The results of determinations of the fragility tests may be found in Tables 1 and 2 with the average for each age group in Table 3. The overall mean values for beginning and for complete hemolysis were computed to be 0.45% and 0.33%, respectively, for the males, and 0.42% and 0.35% for the females.

The results of the reticulocyte counts are given in Tables 1 and 2, the average for each age group in Table 3. The mean value for the male group was calculated to be 0.53%, with values ranging from 0.14% to 1.80%, while the mean values for the females was 0.64%, with values from 0.18% to 1.26%.

Computed Constants. The following indices were computed from the experimentally determined values: The color index, volume index, and the saturation index. Computations were also made of the mean corpuscular hemoglobin, mean corpuscular volume, and of the mean corpuscular hemoglobin concentration.

Color Index. This well-known figure expresses the relative amount of hemoglobin in the erythrocyte as compared with "normal" blood. The "normal" values used were a hemoglobin concentration of 14.5 gm. per 100 cc. and a red cell count of 5,000,000 cells per c.mm. for the males, while for the females we used a red cell count of 4,500,000 cells per c.mm., with the same hemoglobin as "normal." The color indices for the male group ranged from 0.92 to 1.05 with an average value of 0.99, as is shown by Table 1. For the female group, the color index ranged from 0.82 to 1.01, the average value being 0.88 as is

shown by Table 2. Table 3 shows the color indices for the various age groups for both sexes.

Volume Index. The volume index is an indication of the average volume of the red cell, relative to the "normal." For the computation, a "normal" packed cell volume of 48 cc. and an erythrocyte count of 5,000,000 cells per c.mm. were used for the males, and for the females, the "normal" packed cell volume was taken to be 46 cc. with a red

TABLE 1.—EXPERIMENTAL AND CALCULATED VALUES FOR GROUP (MALES)

TABLE 1.—EXPERIMENTAL AND CALCULATED VALUES																
No.	Age	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per cmm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ	Mean corp. Hb., $\gamma\gamma$	Mean corp. Hb. con.	Saturation index	Reticulocytes, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution	
1	65	11.7	80	4.2	0.99	47.3	98.5	1.04	110.2	27.8	24.8	0.91	0.43	0.44	0.36	
2	67	12.3	85	4.4	0.99	42.7	89.1	1.04	100.0	28.1	25.6	0.95	0.22	0.45	0.32	
3	68	12.8	88	4.3	1.02	41.0	85.4	0.99	95.5	29.8	31.2	1.03	1.00	0.42	0.30	
4	69	14.3	99	5.1	0.99	51.1	106.0	1.06	102.0	25.2	28.1	0.93	0.29	0.40	0.32	
5	70	11.4	79	4.1	0.96	37.2	77.5	0.96	90.8	27.8	30.7	1.02	1.18	0.46	0.38	
6	72	9.9	68	3.5	0.97	35.0	72.9	1.04	100.0	25.3	28.3	0.93	0.17	0.40	0.28	
7	73	13.2	91	4.8	0.95	43.4	90.3	0.94	90.0	27.4	30.2	1.01	0.63	0.42	0.32	
8	73	13.6	94	4.8	0.98	47.0	98.0	1.02	98.0	28.3	28.9	0.96	0.63	0.42	0.30	
9	74	15.0	103	4.9	1.05	50.2	104.0	1.06	102.0	30.6	30.0	0.99	0.46	0.44	0.34	
10	74	13.7	94	5.0	0.94	41.0	85.4	1.10	105.0	27.4	33.4	1.10	0.61	0.42	0.28	
11	76	9.7	67	3.4	0.93	42.0	87.5	1.00	95.4	26.8	26.9	0.89	0.53	0.46	0.34	
12	76	11.8	82	4.4	1.01	49.1	102.0	1.07	102.0	28.8	29.1	0.97	0.97	0.67	0.44	
13	76	14.0	96	4.8	1.02	44.0	91.6	0.93	99.0	28.9	29.3	0.97	0.89	0.90	0.44	
14	76	14.5	100	5.0	1.02	43.0	89.6	1.03	108.0	29.4	27.1	0.89	0.99	0.65	0.42	
15	77	12.6	87	4.4	1.01	39.8	82.9	1.14	108.0	28.3	30.0	0.99	0.72	0.44	0.34	
16	77	10.8	74	3.7	0.99	46.0	95.8	1.01	108.0	29.2	27.1	0.95	0.52	0.42	0.28	
17	77	13.8	95	4.9	1.02	45.0	93.8	1.14	100.0	28.3	28.3	0.95	0.68	0.70	0.42	
18	77	12.2	84	4.2	0.98	49.1	102.0	1.03	112.0	29.6	26.4	0.98	0.98	0.50	0.42	
19	78	14.1	97	5.0	0.98	39.4	82.1	1.02	97.5	29.3	28.6	0.95	0.95	0.46	0.34	
20	78	10.4	72	3.5	1.03	40.6	84.5	1.04	100.0	28.8	31.8	1.04	0.39	0.40	0.32	
21	78	12.0	83	4.1	1.01	49.2	102.0	0.94	89.5	28.5	29.9	0.99	0.99	0.46	0.42	
22	78	14.1	97	4.9	0.99	44.0	91.8	1.00	95.6	28.6	34.8	1.15	1.02	0.42	0.28	
23	78	14.0	96	4.9	0.98	44.5	92.8	1.00	84.8	30.0	24.5	0.76	0.67	0.44	0.34	
24	79	13.3	92	4.7	1.00	43.1	89.7	1.26	121.0	29.7	26.6	0.87	0.68	0.42	0.36	
25	79	15.0	103	5.1	1.03	40.0	83.4	1.18	110.0	30.0	26.6	0.91	0.27	0.46	0.36	
26	79	9.8	63	3.3	0.95	40.6	84.6	1.04	103.0	28.2	27.7	0.91	0.41	0.48	0.39	
27	79	10.8	74	3.6	1.03	39.0	81.3	0.92	88.7	28.4	31.9	1.04	0.20	0.44	0.30	
28	79	10.7	74	3.8	0.97	39.0	81.3	0.92	88.7	28.4	31.9	1.04	0.20	0.44	0.30	
29	79	12.8	88	4.5	0.98	44.0	91.6	1.02	97.8	26.5	27.3	0.91	0.20	0.44	0.26	
30	79	12.0	83	4.5	0.92	40.1	83.6	1.11	106.0	28.1	27.7	0.92	0.80	0.42	0.34	
31	80	10.4	72	3.8	0.95	48.1	100.0	1.06	102.0	28.2	25.2	0.95	0.98	0.17	0.40	
32	80	13.3	92	4.7	0.98	39.3	81.8	1.00	95.0	28.3	33.3	1.10	0.40	0.46	0.30	
33	80	11.6	80	4.1	0.98	39.3	81.8	1.00	95.0	28.3	33.3	1.10	0.40	0.46	0.30	
34	80	14.1	97	5.0	0.99	42.2	87.9	0.90	84.8	27.8	33.8	1.12	0.20	0.42	0.32	
35	80	13.7	94	4.9	0.96	40.5	84.4	0.86	87.2	27.6	30.4	0.99	0.55	0.40	0.32	
36	81	13.0	90	4.7	0.98	46.1	95.9	1.02	97.8	28.6	30.4	0.99	0.93	0.83	0.40	
37	81	14.0	96	4.9	0.99	42.5	88.5	0.99	93.9	28.5	28.5	0.93	0.93	0.14	0.42	
38	82	10.0	69	3.5	0.99	35.5	74.0	1.06	100.0	28.4	30.4	1.01	0.22	0.42	0.34	
39	82	12.9	89	4.5	1.00	44.0	91.6	0.98	94.0	29.1	30.5	1.00	0.22	0.42	0.34	
40	83	13.4	92	4.6	1.02	39.3	82.0	0.87	82.5	29.2	35.4	1.17	0.37	0.44	0.36	
41	83	13.9	96	4.8	1.00	42.2	88.0	0.96	91.7	29.0	31.5	1.04	0.46	0.44	0.36	
42	84	13.3	92	4.6	1.00	42.2	88.0	0.96	91.7	29.0	31.5	1.04	0.46	0.44	0.36	
43	84	14.6	101	4.9	1.03	52.2	109.0	1.11	106.0	28.0	27.9	0.92	1.00	0.40	0.30	
44	84	11.2	77	4.0	0.96	40.2	88.1	1.07	103.0	28.6	28.1	0.92	0.93	1.80	0.46	
45	85	11.7	80	4.1	0.98	43.3	90.2	1.05	100.0	28.9	32.1	1.06	0.27	0.44	0.36	
46	86	12.1	84	4.3	0.98	43.0	89.5	0.95	90.0	28.7	34.9	1.15	0.40	0.42	0.30	
47	87	13.8	95	4.8	1.01	40.1	83.6	0.87	82.4	28.7	35.4	1.16	0.28	0.44	0.30	
48	88	14.0	97	4.9	1.00	40.4	84.2	0.88	81.3	28.3	29.0	0.95	0.95	0.57	0.45	
49	91	14.3	98	5.0	1.00	40.2	83.8	0.95	83.8	28.3	29.0	0.95	0.95	0.57	0.45	
50	91	13.0	90	4.5	1.03	40.2	83.8	0.95	83.8	28.3	29.0	0.95	0.95	0.57	0.45	
Av.		78.3	12.65	87.3	4.4	1.00	41.2	85.8	1.02	97.7	28.5	29.6	0.98	0.57	0.45	0.37

cell count of 4,500,000. The volume index is equal to the percentage of packed cells (see above), divided by the ratio of the red cell count to the "normal." The computed male values ranged from 0.85 to 1.26 with 1.02 as the mean value, and the female values from 0.66 to 1.20, with a mean value of 0.88.

Saturation Index. This is an indication of the amount of hemoglobin per unit volume of erythrocyte relative to the "normal." It is

TABLE 2.—EXPERIMENTAL AND CALCULATED VALUES FOR THE FEMALE GROUP

No.	Age	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb., %	Mean corp. Hb. con.	Saturation index	Reticulocytes, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
1	66	10.4	72	3.6	0.90	35	76	0.95	97	29.0	29.9	0.95	0.43	0.42	0.30
2	68	11.6	80	4.2	0.86	30	65	0.70	72	27.8	33.1	1.23	0.29	0.40	0.32
3	69	9.8	68	3.3	0.93	25	54	0.74	67.5	26.5	39.2	1.26	0.50	0.44	0.36
4	69	12.8	88	4.3	0.93	37	80	0.84	88	29.8	34.9	1.10	0.63	0.44	0.34
5	70	13.0	90	4.7	0.87	40	87	0.84	86	27.9	32.5	1.03	0.32	0.42	0.28
6	70	11.7	81	4.0	0.91	32	70	0.79	80	29.2	31.6	1.15	0.18	0.42	0.34
7	71	14.1	97	4.8	0.92	46	100	0.93	96	29.3	30.7	0.97	0.29	0.46	0.36
8	71	12.2	84	4.5	0.84	38	83	0.83	84	27.1	32.1	1.01	0.41	0.44	0.34
9	71	10.8	74	3.9	0.86	39	85	0.98	100	27.0	27.9	0.87	0.50	0.40	0.32
10	73	13.6	94	4.6	0.92	44	96	0.94	96	29.5	30.9	0.98	0.38	0.42	0.28
11	73	12.9	89	4.5	0.89	38	83	0.83	85	28.8	33.0	1.07	0.26	0.40	0.32
12	73	11.8	81	4.1	0.88	36	78	0.85	87	28.7	32.9	1.04	0.85	0.40	0.30
13	75	9.9	68	3.6	0.85	27	59	0.73	75	27.4	36.7	1.15	0.67	0.42	0.34
14	75	10.4	72	3.6	0.90	32	70	0.88	89	28.9	32.5	1.03	1.02	0.44	0.36
15	75	12.2	84	4.3	0.87	36	78	0.81	94	28.3	33.9	1.07	0.64	0.42	0.32
16	75	11.0	76	3.9	0.88	41	89	1.03	105	28.4	26.9	0.86	0.31	0.40	0.32
17	76	14.9	103	5.0	0.93	47	102	0.92	96	29.9	31.7	1.01	0.48	0.44	0.36
18	76	16.0	114	5.2	0.94	52	113	0.97	100	30.7	30.8	1.01	0.50	0.42	0.32
19	76	10.0	69	3.5	0.88	29	63	0.81	83	28.6	34.5	1.09	0.48	0.40	0.28
20	76	12.3	85	4.4	0.87	38	83	0.85	86	27.9	32.4	1.02	1.26	0.44	0.32
21	76	10.4	72	3.8	0.86	34	74	0.88	91	27.7	30.6	0.98	0.21	0.42	0.30
22	76	9.9	68	3.3	0.93	29	63	0.86	88	30.0	33.1	1.08	0.55	0.40	0.34
23	76	11.2	77	3.4	1.01	42	91	1.20	123	32.8	26.7	0.85	0.78	0.42	0.34
24	77	14.0	96	4.9	0.88	46	100	0.92	94	28.5	30.5	0.96	0.69	0.42	0.32
25	77	11.9	82	4.5	0.82	38	83	0.83	84	26.5	31.3	0.99	0.74	0.40	0.32
26	77	12.3	85	4.4	0.87	40	87	0.89	91	27.9	30.6	0.93	0.41	0.44	0.36
27	77	10.5	72	3.8	0.85	37	80	0.94	97	27.3	28.4	0.90	0.32	0.40	0.28
28	77	12.3	85	4.1	0.93	36	78	0.86	88	30.0	34.2	1.09	0.51	0.42	0.34
29	78	11.5	79	4.0	0.84	38	83	0.93	95	28.6	30.3	0.95	0.80	0.44	0.36
30	78	10.0	69	3.4	0.91	30	65	0.86	88	29.3	33.3	1.06	0.93	0.44	0.34
31	78	7.8	68	3.3	0.93	27	59	0.81	82	30.0	36.3	1.15	0.34	0.42	0.32
32	78	9.9	68	3.6	0.87	30	65	0.83	86	28.2	33.0	1.04	0.91	0.40	0.34
33	78	12.6	87	4.7	0.83	38	83	0.79	81	26.7	33.1	1.05	0.77	0.44	0.38
34	78	13.1	90	4.7	0.87	35	76	0.74	76	28.2	37.4	1.18	0.88	0.40	0.30
35	79	11.8	81	4.3	0.85	29	63	0.66	67.5	27.5	40.7	1.28	0.21	0.42	0.34
36	79	13.8	95	4.5	0.95	41	89	0.89	91	30.6	33.7	1.04	0.18	0.44	0.36
37	79	10.6	73	3.3	1.00	39	85	1.16	118	32.1	27.2	0.86	0.62	0.44	0.36
38	79	10.1	70	3.6	0.88	34	74	0.92	94	28.0	29.7	0.95	0.49	0.42	0.34
39	79	13.7	94	4.8	0.88	40	87	0.81	83	28.4	34.3	1.08	0.17	0.44	0.36
40	81	14.1	97	4.8	0.92	44	96	0.90	92	29.4	32.1	1.01	0.65	0.40	0.30
41	84	14.6	100	4.9	0.92	47	102	0.94	96	29.8	31.1	0.98	0.79	0.42	0.38
42	84	10.0	69	3.5	0.90	29	63	0.82	83	28.9	34.5	1.09	0.44	0.40	0.32
43	86	9.5	66	3.4	0.88	26	57	0.76	77	28.2	36.5	1.15	0.81	0.44	0.36
44	87	9.9	68	3.5	0.87	31	67	0.86	88.5	28.4	31.9	1.01	0.98	0.42	0.30
45	89	12.6	87	4.2	0.94	38	83	0.89	90	29.9	33.2	1.05	0.51	0.44	0.34
46	89	11.9	82	4.1	0.90	32	70	0.77	78	28.9	37.2	1.17	0.42	0.42	0.36
47	90	10.8	76	3.9	0.94	41	89	1.03	105	27.9	26.4	0.91	0.60	0.40	0.32
48	90	11.2	77	3.9	0.88	40	87	1.00	102	28.6	28.0	0.88	0.33	0.46	0.36
49	93	9.5	66	3.2	0.93	30	65	0.92	94	29.7	31.7	1.01	0.61	0.42	0.28
50	104	10.1	70	3.5	0.89	33	72	0.91	93	28.5	30.6	0.97	0.90	0.44	0.34
Ar. 77.2		11.7	80.5	4.1	0.88	36.7	80	0.88	90.0	28.8	32.3	1.00	0.64	0.42	0.35

calculated by dividing the per cent hemoglobin by the percentage "normal" of the packed cells. The values varied from 0.76 to 1.17 for the males, and from 0.85 to 1.28 for the females. The average male saturation index was 0.98 and the average female saturation index was 1.0.

TABLE 3.—EXPERIMENTALLY DETERMINED AND COMPUTED VALUES FOR VARIOUS AGE GROUPS

Age group	Hb, gm. per 100 cc.	Hb, %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb, $\gamma\gamma$	Mean corp. Hb, com. %	Saturation index	Retiocytes, %	Hemolysis starts, % salt solution	Hemolysis complete, % R.T. solution
							FEMALE							
65-69	11 2	77 4	3 9	0 90	32	70	0 81	81 1	28 3	34 4	1 13	0 46	0 42	0 33
70-74	12 6	87	4 5	0 89	40	86	0 88	89 6	28 5	31 2	1 01	0 33	0 42	0 32
75-79	11 7	81	4 1	0 89	36	79	0 96	90 0	28 9	32 4	1 02	0 59	0 42	0 33
80-84	12 9	89	4 4	0 92	40	87	0 88	90 6	29 4	32 6	1 02	0 63	0 41	0 30
85-89	11 0	76	3 8	0 90	32	69	0 82	81 1	28 8	34 7	1 09	0 68	0 43	0 34
90-94	10 5	72	3 7	0 91	37	81	0 98	100 0	28 7	28 7	0 93	0 51	0 42	0 32
95+	10 1	70	3 6	0 89	33	72	0 91	93 0	28 5	30 6	0 97	0 90	0 44	0 34
							MALE							
65-69	12 8	88	4 5	1 00	45 5	95	1 03	102 0	28 5	28 2	0 93	0 48	0 43	0 32
70-74	12 9	89	4 5	0 98	42 3	88	0 98	95 7	28 3	30 2	1 00	0 62	0 43	0 31
75-79	12 4	86	4 3	0 99	42 9	89	1 09	101 0	28 7	28 9	0 95	0 57	0 43	0 32
80-84	12 9	89	4 5	0 99	43 0	90	0 99	93 0	28 5	30 3	1 00	0 49	0 43	0 33
85-89	12 5	96	4 5	0 99	41 7	87	1 01	95 1	28 5	30 1	0 99	0 90	0 44	0 32
90-95	13 6	94	4 7	1 01	40 3	84	0 91	85 5	28 9	33 8	1 12	0 22	0 42	0 33

These indices are to be found in Tables 1 and 2, with the mean values for the different age groups of both sexes in Table 3.

Mean Corpuscular Volume. This figure represents the volume of the average erythrocyte in cubic micra, and is computed by dividing the absolute volume of packed cells per 1000 cc. of blood, by the cell count in millions per c.mm. The mean corpuscular volume in the male subjects ranged from 81.3 cu. micra to 121 cu. micra, with a mean value of 97.7 cu. micra, and that for the females from 67.5 to 123 cu. micra, the mean value being 90 cu. micra.

Mean Corpuscular Hemoglobin. This is the average weight of hemoglobin in each red cell, expressed in micromicrograms. (A $\gamma\gamma$ is equal to 1×10^{-12} gm.) It is equal to the grams of hemoglobin per 1000 cc. of blood divided by the red cell count in millions per c.mm. Our male subjects showed a mean corpuscular weight between 26.5 and 30.6 micromicrograms, while the mean weight for the females was from 26.5 to 32.1 micromicrograms. The average values fell at 28.5 micromicrograms for the males and 28.8 micromicrograms for the females.

Mean Corpuscular Hemoglobin Concentration. This value is a measure of the average concentration of the hemoglobin in the erythrocyte, expressed as a percentage. It is computed by dividing the grams of hemoglobin per 100 cc. of blood by the volume of packed cells in cc. per 100 cc., and multiplying the resulting decimal by 100. The range of values for the male group was between 24.5 and 35.4%, the average

being 29.6% and for the females, between 26.4% and 40.7%, with an average of 32.3%.

All of the above mentioned values may be found in Tables 1 and 2, with the average for each age group in Table 3.

Discussion. These experimentally determined and computed values, to the best of our knowledge, comprise the first study in a group of this type using the computation of all the hematologic constants.

The findings presented in this paper may be compared with values appearing in the literature for comparable groups, by referring to Table 4. In Table 4, we have outlined the results of investigations by several observers into the hemoglobin, erythrocyte counts, and hematocrit readings of normal individuals past 60 years of age.

TABLE 4.—COMPARISON OF RESULTS OBTAINED BY DIFFERENT INVESTIGATORS

Authors	Ref. No.	Age group	Sex	Hb.	RBC	Packed cells	Remarks
Leichenstern	8	60 and up	M	14 3			Cited by Kilduffe
			F	13 1			
Williamson	28	61-70	M	16 3	Spectrographic method
		71-75	M	15 5			
		61-70	F	15 8			
		71-75	F	15 3			
Cameron and Nielolson	2	60-70	M	16 1			
		71-75	M	15 2			
		75-	M	15 7			
		66-70	F	15 6			
		71-75	F	15.4			
		75-	F	15 1			
Nelson and Stoker	13	60 and up	M	15 5	5 22		
Miller	12	60 and up	M	14 3	4 46		
Fowler <i>et al.</i>	4	60 and up	M	13 1	4.61	41 4	Also found that the presence or absence of free HCl in the stomach had no bearing on the blood findings
			F	11 9	4 47	40 0	
Newman and Gitlow		65 and up	M	12 7	4 42	41 2	
			F	11.7	4.10	36.7	

In reviewing the early literature, we were struck by the fact that no differentiation was made between the sexes when hematologic studies were done on individuals past 60 years of age. Whether this is due to the small number of cases reported upon, and hence the necessity for grouping the males and the females for a statistically reliable number of cases, we do not know. It is known that young healthy females have normal values for hemoglobin, erythrocytes, and hematocrit readings that are lower than the corresponding values for males. Several theories have been advanced to account for this.^{3,9,15} But when we study the results of investigations into the hematologic sex differences in the aged, none of these theories seem to explain these differences satisfactorily. The theory of the loss of iron during menstruation does not explain the lower hemoglobin of a group of 80-year old women than that shown by a group of 80-year old men. The explanation that younger women lead a less active life than the men and hence need less hemoglobin to transport the oxygen necessary for their metabolic processes may possibly be true; but both aged men and aged women lead sedentary lives. Probably for females below the age of menopause, both these factors are involved. In any case,

these sex differences that are found in the aged may be a carry-over from younger days. That such a difference does in fact exist in the aged, may be seen from an inspection of Table 5, wherein we have presented the average findings of this study for both sexes together with the standard deviations and probable errors, in order to show that the ratio of the difference between the means to the square root of the sum of the squares of the probable errors is considerably greater than 6, which is the criterion for statistical significance.

TABLE 5.—COMPARISON OF RESULTS FOR MALES AND FEMALES

	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb., %	Mean corp. Hb. con. %	Saturation index	Reticulocyte count, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
$M\sigma$	12.7	87.5	4.42	0.99	41.2	85.8	1.02	97.7	28.5	29.6	0.98	0.53	0.45	0.33
S.D. σ	1.48		0.153		4.27		0.086	8.5	0.85	2.61				
P.E. σ	0.0199		0.0021		0.0576		0.0012	0.115	0.0115	0.0332				
$M\varphi$	11.7	80.5	4.10	0.88	36.7	80.0	0.88	90.0	28.8	32.3	1.0	0.64	0.42	0.35
S.D. φ	1.62		0.176		6.05		0.101	20.9	1.28	3.06				
P.E. φ	0.0218		0.0024		0.081		0.014	0.283	0.0173	0.0413				
$M\sigma - M\varphi$	33		98		46		80	27	15	50				
$\sqrt{P.E.^2\sigma + P.E.^2\varphi}$														

$M\sigma$ = Average male value

S.D. σ = Standard deviation for males

P.E. σ = Probable error for males

$M\varphi$ = Average female value

S.D. φ = Standard deviation for females

P.E. φ = Probable error for females

The expression $\left(\frac{M\sigma - M\varphi}{\sqrt{P.E.^2\sigma + P.E.^2\varphi}} \right)$ is the criterion for statistical significance. It should be greater than 6

Perusal of Table 4 brings out several interesting facts. First, as the reports approach the present, the mean values for the various studies seem to become lower. This may be due to an improvement in method, or with the increase in food processing that has taken place of recent years, the iron intake may be actually lower than it has been. Second, the results of studies made by Fowler *et al.*,⁴ Miller,¹² and by us, seem to indicate that the physiologic "normals" for the aged, as reported in several textbooks as well as in the literature are too high. Hence, in reporting the hemoglobin, in view of the controversy over what is "normal" for the aged, results should be stated in terms of grams per 100 cc., and when the various hematologic constants are calculated, the "hemoglobin coefficient" be used as 100%. The "hemoglobin coefficient" is the grams of hemoglobin per 100 cc. of blood calculated to an erythrocyte count of 5,000,000 in the case of males, and to a count of 4,500,000 in the case of females.

The number of red cells in the blood of healthy males is usually thought to average in the neighborhood of 5,000,000 cells per c.mm. The average number of red cells for young healthy females is around

4,500,000 cells per c.mm. Our data for both males and females fall below these values. The work of Fowler *et al.*⁴ likewise points to a lower average value. It should be noted that in spite of the slight difference between the mean value of the erythrocyte count in the male and that in the female, Table 5 shows that the difference is real and statistically significant.

A great difference may be seen to exist between the male and female "normal" hematocrit values and the corresponding mean values determined by us. Similarly, Fowler *et al.*⁴ working with 100 males past the age of 60 years, found that the hematocrit readings averaged 41.4 cc. of blood. Hence, it is the opinion of the authors that instead of 48 or 46 cc.²⁹ being used as the "normal" hematocrit reading for aged males or females, the value, 42 cc. would seem to represent a truer normal male value, while for the females, a still lower average normal, about 38 cc. be used. (Osgood and Wilhelm¹⁶ report a mean packed cell volume of 42 cc. for young healthy males.)

The mean corpuscular volume as determined for young healthy individuals and reported by Wintrobe²⁹ is 87 cu. micra. The mean value found by us for the male subjects namely, 97.7 cu. micra, as well as the mean values for the females, 90 cu. micra, are both larger than this value. Table 5 shows the difference between the male and female mean values to be truly significant.

Wintrobe²⁹ likewise reported that the mean corpuscular hemoglobin was from 27 to 32 micromicrograms. Our mean values for either sex fall within these limits. Despite the small difference between the means (28.5 $\gamma\gamma$ for the males, and 28.8 $\gamma\gamma$ for the females), the difference is truly significant (Table 5).

The normal variation for the mean corpuscular hemoglobin concentration has been reported as from 32% to 38%.²⁹ Our mean male value of 29.6% is lower than this, while the mean female value of 32.3% falls just within these limits.

Haden⁶ has shown that the diminished resistance of erythrocytes to hypotonic salt solutions is probably not due to any abnormality in the chemical make-up of the cell, but rather to changes in its shape. When the red cells are immersed in a hypotonic salt solution, they change from a flat biconcave disk to a sphere before rupture occurs. The more nearly spherical they are to begin with (as in the case of hemolytic jaundice, where spherocytosis is pronounced), the less they can swell before rupture of the cell membrane takes place. Our subjects showed normal resistance to hypotonic saline solutions. It may therefore be reasoned that the shape of their cells is similar to the shape of the cells in younger healthy individuals. Furthermore, the normal values reported elsewhere for fragility studies may be applied with safety when dealing with the blood of individuals past 65 years of age. Various observers present values for the reticulocyte percentage in normal individuals ranging all the way from less than 0.1% up to more than 2%.^{1, 6a, 10, 22, 27} Our data fall in between these two values. We could find no correlation between the percentage of reticulocytes and any other determined or computed value. This was to be expected,

since the formation of new erythrocytes is independent of the circulating cells.

No significance could be attached to the difference between the sexes as far as the values for the saturation index, the reticulocyte count, or the resistance of the erythrocytes to hypotonic saline.

It should be stated at this point, that several of the experimental group presented findings that at first glance are open to diagnostic question: For example, Male Subject 11 showed a volume index of 1.10, using the usually accepted normal values, and a slightly elevated mean corpuscular volume. This is suggestive of a pernicious anemia. However, since the subject showed no other signs or symptoms, and in view of the color index, which was below 1, the individual was treated as a normal. Similarly for Male Subject 31. Low values for the various indices, as for example Male Subject 10 with a volume index of 0.85, No. 35 with a volume index of 0.86, and No. 41 with a volume index of 0.87, were treated as low normals, in view of the normality of the other findings, rather than secondary anemias.

In a subsequent paper, we shall present our findings dealing with a study of the leukocytes of the normal aged individual.

Conclusions. 1. Determinations were made of the hemoglobin, the erythrocyte count, the volume of packed cells, the reticulocyte count, and the resistance of the red cells to hypotonic salt solutions in a group of 100 individuals past 65 years of age.

2. The color index, volume index, saturation index, the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration were computed.

3. Comparisons were made with "normal" values reported by other observers.

4. It was found that the physiologic "normals" should be modified when dealing with aged individuals.

5. There is a statistically significant difference between the male and female values as determined by us for hemoglobin, red cell count, hematocrit readings, volume index, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

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A STUDY ON THE VALUE OF A MIXED BACTERIAL "ORAL COLD VACCINE"

BY MORRIS SIEGEL, M.D.

MARIAN G. RANDALL, R.N.

MURIEL D. HECKER, M.A.

AND

MABEL REID, M.A.

NEW YORK, N. Y.

(From the Division of Infectious Diseases of The Public Health Research Institute of
The City of New York, Inc., and the Henry Street Visiting Nurse
Service of New York City)

As is true of a number of virus diseases, the common cold acquires clinical and pathologic significance because of the secondary complications arising from superimposed bacterial pathogens. Since prophylactic immunization directed in this case towards the virus itself is not at present attainable, attempts have been made to solve the problem by reducing the number or severity of the secondary complications by artificially increasing resistance to the potentially virulent bacteria of the upper respiratory tract. Vaccines of mixed bacteria administered by one route or another have been given experimental trials, but as yet the results reported have been of varying success.¹⁻¹⁵ The desire to protect its personnel against recurring colds induced the Visiting Nurse Service of New York City to undertake a study of its own on the effectiveness of bacterial vaccines in preventing the more usual respiratory complications. The conditions seemed to be par-

ticularly favorable for a satisfactory test since daily reports could be made available on a group of cooperative individuals whose work exposed them frequently and intimately to acute respiratory infections.

Plan of Study. The Henry Street Visiting Nurse Service provides home nursing care for the sick. About 500,000 visits to approximately 100,000 cases are made each year. The personnel consists of about 300 nurses and 70* office workers distributed among 15 centers in Manhattan, The Bronx, and Queens, and an administration office in Manhattan.

The study was limited to volunteers of the nursing and office staffs. About 70% of the personnel volunteered. They were divided into 2 groups depending upon the number of colds experienced in the preceding year. Each group was further subdivided into those with (a) chronic sinusitis, bronchitis, or otitis, (b) allergies and (c) no clinical manifestations—making 6 classifications in all. The names of those in each classification were sorted according to branch office. Within each office, the individuals studied were arranged alphabetically by name and allocated alternately to control and test groups without their knowledge.

For purposes of immunization a commercial product composed of mixed, heat-killed bacteria (i. e., about 25 billion pneumococci, 15 billion streptococci, 5 billion *H. influenzae*, and 5 billion *M. catarrhalis* per dose) was prepared in the form of capsules to be taken orally. The control group, on the other hand, was given capsules identical in appearance and containing the same ingredients without bacteria.† Both types of capsules were distributed in the same kind of container labeled with identical directions for use and containing enough capsules for the entire test period. Single capsules were taken daily for the first 14 days, and twice weekly thereafter, as recommended by the producer and distributor of the product.

Each day a report was made of the number of capsules taken, of any symptoms of infection of the respiratory tract, and of any days off duty because of respiratory illness. The data were contained in the regular report of activities which are recorded daily by the personnel. Punch cards and machine tabulators were used to collect and analyze the data.

The test period lasted from September 3, 1940 through March 30, 1941, a period of 210 days. It began 14 days after the first capsule was taken on August 19, and ended on March 30 for those completing the study, or before March 30 for those who dropped out. A summary of the number of individuals in each group and of the number of person-periods of observation follows:

TABLE 1

	Group		
	Test	Control	Total
Number of persons in study:			
Total	125	128	253
Duration of observation:			
Entire period (210 days)	71	76	147
Part of period (less than 210 days)	54	52	106
Number of person-periods‡ of observation.	112	111	223

The groups were almost equal in size and in duration of follow-up. They were comparable in regard to the number and duration of respiratory infections in the preceding year, and in the number of days off duty on account of such illnesses. About 95% of the individuals were from 25 to 40 years of age.

* This number includes members of departments serving both the Visiting Nurse Service and the Henry Street Settlement.

† We wish to thank Eli Lilly & Co. for supplying both forms of capsules used in the study.

‡ On the basis of 210 days per person.

Results. Each group had 239 colds during the test period in 1940-41. A summary of the number of colds in 1940-41 among those with "few" (less than 3) or "many" (3 or more) colds during the same period of the preceding year follows:

TABLE 2

No. of colds during test period (1940-41)	Total		Those with less than 3 colds in year preceding test period		Those with 3 or more colds in year preceding test period	
	Test group	Control group	Test group	Control group	Test group	Control group
0	20	16	9	9	11	7
1	29	40	14	19	15	21
2	42	40	14	20	28	20
3	17	16	8	4	9	12
4	10	10	5	2	5	8
5	7	5	3	1	4	4
6	0	1	0	0	0	1
Total (persons)	125	128	53	55	72	73
Person-periods of observation	112	111	50	49	62	62
Colds	239	239	101	84	138	155
Colds per person-period	2.1	2.2	2.0	1.7	2.2	2.5

Among those with 3 or more colds in the preceding year, fewer colds were reported during the test period by 54 (75%) of the inoculated and 48 (66%) of the controls. Among those with less than 3 colds the year before, more colds were reported during the period of observation by 16 (30%) of the inoculated and 7 (13%) of the controls. The number of colds per person-period of observation during the test period was 2.1 for those receiving the vaccine and 2.2 for those taking the control capsules. It was slightly higher for the inoculated than the controls among those with less than 3 colds in the preceding year, and slightly lower for the inoculated than the controls among those with 3 or more colds in the preceding year.

The average duration of symptoms experienced by the group taking the vaccine was 10.5 days per cold, as compared with 9.7 days for the control group. On the whole, the duration of symptoms was longer than that reported in most other studies, partly because symptoms were recorded daily and partly because symptoms recurring within a period of less than 7 days were not attributed to a new cold but to the old one.

The number of days of absence during the test period on account of respiratory illnesses varied from 0 to 43. The distribution of the inoculated and controls according to the number of days of absence is shown in Table 3.

About 33% of the persons in each group had no absences. An additional 25% to 30% were absent from 1 to 2 days, and about 15% to 20% from 3 to 4 days. In all, 80% of the inoculated and 76% of the controls had from 0 to 4 absent days during the 7-month period of observation. About 13% in each group were absent from 5 to 7 days, and 8% from 8 to 21 days. The distribution of inoculated and control persons according to the number of days absent was, therefore, fairly parallel over the range from 0 to 21 days which included all of the

inoculated and 98% of the controls. Three controls, comprising 2% of the group, were absent 25, 40, and 43 days, respectively, a total of 108 days. They increased by 30% the number of absent days in the control group, and raised the arithmetic average for the group to 4.2 days per person-period of observation as compared with 3.1 for the inoculated. On the other hand, the median values for the groups were 2.0 and 2.2 absent days respectively, for inoculated and control individuals.

TABLE 3

No. of days absent during test period	Test group		Control group	
	No.	% distribution	No.	% distribution
0	42	33.6	42	32.8
1-2	40	32.0	31	24.2
3-4	18	14.4	24	18.8
5-7	15	12.0	17	13.3
8-14	7	5.6	8	6.3
15-21	3	2.4	3	2.3
22-43	0	0.0	3	2.3
Total (persons)	125	100.0	128	100.0
Person-periods of observation	112	..	111	
Days absent:				
(a) Total	342	.	462	
(b) Average	3.1	.	4.2	
(c) Median	2.0	.	2.2	

About 40% of the illnesses in each group appeared to be uncomplicated head colds and about 60% were somewhat more severe or associated with complications. A summary of the latter cases in each group follows:

TABLE 4

Nature of illness	Total	Test group	Control group
Bronchitis	86	41	45
Grippe or influenza	55	26	29
Otitis	11	7	4
Pneumonia	3	2	1
Tonsillitis	110	56	54
Total cases	265	132	133

The cases which had complications or were considered more severe than a head cold were fairly evenly distributed between the two groups.

During the period of observation, a few persons in the control and inoculated groups volunteered the opinion that they were being helped by the capsules taken. Unfortunately, a survey on this point was not made at the end of the study before the names in each group had been announced.

Comment. The evidence outlined in this report indicates that the oral administration of a commercially prepared vaccine of mixed killed bacteria as described above failed: (1) to decrease the incidence of acute respiratory infections, (2) to reduce the severity or duration of such infections, and (3) to prevent secondary bacterial complications. A group of individuals observed for purposes of control ran remarkably similarly to those receiving vaccines. Thus, both control and inoculated groups had exactly the same number of colds, and there

was no significant difference between the groups in the duration of symptoms and in the number and variety of complications following the colds. These observations strengthen those already made by various investigators^{1,4,5,11} that contrary to fairly widespread medical and lay opinion so-called "cold vaccines" are of questionable value as a prophylactic measure both against the common cold and its bacterial complications.

Since the method of immunization was *per os*, it may be that antibody formation may not have been adequate; or it may be as Walsh^{13,14} postulates, that the immunity stimulated in such cases must be local (*i. e.*, stimulated by application of the vaccine topically to the membranes of the upper air passages). However, the latter assumption is based on inconclusive data, and if true then it must be assumed that immunity to bacteria of the respiratory tract belongs to a special category, since general methods of administration of vaccines such as subcutaneous, intramuscular, intraperitoneal, and intravenous have been successful in inducing prophylactic immunization in a variety of infections.

On reflection, it is difficult to see why a bacterial vaccine composed of a few arbitrarily selected organisms, administered by any route, can be effective against the greater bulk to which the respiratory tract is exposed. The specific effects of such vaccines are limited to the relatively few bacterial types of the species employed since no consideration is made of the multiplicity of types of streptococci, pneumococci, and other pathogenic microorganisms. Furthermore, the non-specific effects of the vaccine are of questionable value and, therefore, not dependable. However, in the face of continued recommendations based on personal experiences from both physicians^{2,8,9,10} and lay people, it became necessary to derive definite information from a controlled study. As reported above, this has ended with the contrariwise opinion of the ineffectiveness of "oral cold vaccines."

Conclusions. The oral administration of a heat-killed vaccine containing several species of potentially pathogenic bacteria of the upper respiratory tract appeared to have no influence either on the incidence or severity of the common cold. Similarly, no effect was observed as a result of this treatment on the secondary complications frequently associated with the common cold. A group of control individuals receiving similar preparations without bacteria paralleled closely in almost every way the infections observed in the individuals receiving the vaccine.

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HEMOTHORAX IN BLOOD DYSCRASIAS

BY PAUL FREEDMAN, M.D.

CAPTAIN, M. C.

SAMUEL LEVINE, M.D.

AND

LEON SOLIS-COHEN, M.D.

PHILADELPHIA, PA.

(From the Department of Radiology of the Jewish Hospital)

THOUGH the blood dyscrasias associated with abnormal tendency toward bleeding, such as the purpuras, scurvy, and hemophilia are usually mentioned as possible causes of non-traumatic hemothorax, actual case references in the literature are rare.

Prior to 1900, there were two such references: Kempf,² who described hemothorax complicating a case of scurvy; Pitt,^{3,4} who, in reviewing 65 cases of hemothorax, mentioned 1 associated with purpura.

Since 1900 there appear to have been no such cases described.¹ Consequently, it was deemed advisable to report 2 cases of hemothorax which were admitted to the Jewish Hospital in a period of 2 months. Both occurred in males, 1 due to hemophilia, and 1 to thrombocytopenic purpura.

It is to be noted, of course, that a distinction is to be made between true blood in the pleural cavity and a pleural effusion, which is blood stained or hemorrhagic. The latter is not uncommon and is frequently seen accompanying malignant and lymphoblastomatous disease of the intrathoracic structures. The former, however, in the pure form, on a non-traumatic basis, is uncommon.

Case Studies. CASE 1. L. S., a 22 year old white male was admitted to the Jewish Hospital in February 5, 1936, complaining of intense anterior left chest pain of about 36 hours duration. The pain was spontaneous in onset, accentuated by motion and respiration, associated with marked pallor, and followed by the passage of two tar-colored stools. Past history revealed that in 1928, at the age of 14, he bled continuously for about 4 weeks after a tonsillectomy. In 1933, following a tooth extraction he again bled profusely, and at the time it was discovered that he was a hemophiliac. Family history indicated that there was a strong background of hemophilia on the maternal side, the paternal relatives were free of the disease (Fig. 1).

On admission he appeared exsanguinated, slightly cyanotic, and restless. The pulse rate was 80, respiratory rate 26, temperature was 97°, and the blood pressure was 80/20. There were signs of fluid in the left chest. Right chest was clear, and heart was displaced to the right. He was transfused several times. Two days after admission, 450 cc. of blood, fluid in character, was

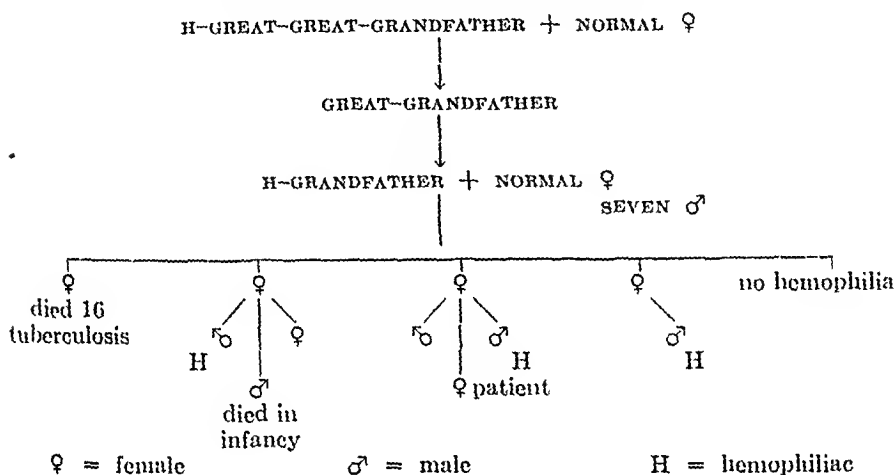
obtained from the left pleural cavity. The next day 500 cc. was removed and a day later 400 cc. was removed. During this period, he received numerous small transfusions. Following this, the patient gradually improved, his respiratory distress disappeared and his bleeding ceased. He was discharged about 30 days after admission, much improved.

	Bleeding time	Clotting time
Feb. 6	5½ min.	3½ min.
Feb. 7	4½ min.	3¼ min.
Feb. 19	4½ min.	5 min.

Other laboratory data were non-contributory.

N.B.—Unusual values in hemophilia.

FIG. 1.—Family tree of Case 1
MATERNAL SIDE OF FAMILY



Roentgen Examination of Chest (Fig. 2) (February 6). There is a homogeneous density extending from left apex to base. The diaphragmatic shadow is obliterated. The heart and trachea are displaced to the right. The rib shadows are not obscured.

Conclusions. Complete left hemothoracic effusion, probably blood.

February 28: Considerable absorption of pleural effusion. Heart and trachea now in normal position. Density along left upper lateral chest wall probably due to residual encysted effusion (Fig. 3).

CASE 2. A. G., a 26 year old white male was admitted to the Jewish Hospital on April 3, complaining of epistaxis of 2 days duration, spontaneous in onset. He had had similar but milder episodes in the previous 12 years, and had always demonstrated a bleeding tendency. There was no relevant familial history, nor any history of drug intake. On physical examination numerous ecchymotic areas of various ages were present over both arms and legs, and bleeding from the nose had ceased. Heart and lungs were natural. Liver was felt 3 cm. below costal margin, the spleen was just barely palpable and was tender in percussion. Except for a moderate hypochromic anemia, a leukopenia, laboratory studies revealed a thrombopenia. On successive days, platelet count was 2200, 2300, 2750 and 2500/mm³. Coagulation time was 3½ minutes, 1 hour +. He was given daily intramuscular injections of thromboplast, in daily intravenous doses of calcium gluconate and repeated blood transfusions.* One dose of Roentgen ray over splenic area was given (186 Kvp, 30 ma., 1/2 Cu 2 Al, 50 cm., 80 R"). He was discharged improved on April 26, 1936, with a platelet count of 11,000.

He was readmitted on May 6, suffering from blood loss. During the interval he had received splenic irradiation. However, on May 3, he began to have

* Some of this and subsequent therapy has been subsequently shown to be empiric.

tarry stools, and subsequently became progressively weaker. On admission, he gave evidence of chronic exsanguination, râles and dullness were present at



FIG. 2.—Note the massive left pleural hemothorax producing marked cardiac and mediastinal displacement to the right.



FIG. 3.—There is partial absorption of the hemothorax which is now loculated.

both pulmonic bases, the abdomen was slightly distended and the spleen barely palpable. Again there was a marked hypochromic anemia (Hgb., 4.3 gm.) and leukopenia (white blood count was 950); platelet count was 5250.

Treatment was similar to that on the previous admission including thromboplastin, direct blood transfusions, cevitic acid, moccasin snake venom as well as liver extract.

On May 11, 5 days after admission, there were clinical evidences of fluid in the left chest. On May 18, there was evidence of displacement of the mediastinum to the right and respiratory embarrassment appeared. On that date, by thoracentesis 450 cc. of bloody fluid was obtained, and on May 21, 150 cc. of similar fluid was removed. Shortly afterward patient's temperature began to fluctuate in a septic fashion. Apparently unrelated to transfusions he began to have chills, abdomen became distended and blood was noted in the stools. On May 25, incision and drainage of left chest yielded greenish yellow pus. Culture subsequently revealed presence of *S. aureus*, and patient was given bacteriophage in addition to other measures. However, his septic course continued, though blood cultures were always negative, and on June 10 he died. Postmortem revealed intestinal mucous membrane hemorrhages, perforated left diaphragm, left sanguinopurulent empyema, necrosis of left lower lobe of lung. No bone marrow studies were done.

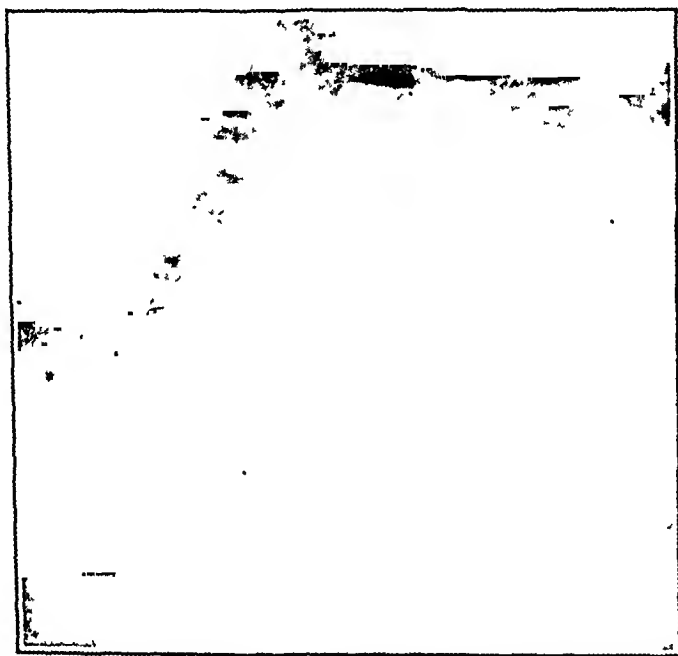


FIG. 4.—Massive left pleural effusion with considerable cardiac displacement to the right.

Roentgen Examination of Chest (Fig. 4). Almost complete uniform density from apex to base of left hemithorax. Heart is displaced to the right.

Conclusions. Pleural effusion, probably blood.

Discussion. Two cases of hemothorax occurring in males of the third decade with an abnormal bleeding tendency are presented. In neither was it a primary manifestation of the disease. In the hemophilic it was acute in clinical onset, while in the purpuric it was more insidious. As is indicated by the course in the former it is not necessarily fatal. The extreme danger of infection which may be introduced from without is emphasized by the outcome in the latter. Therapy, as in all cases of hemothorax is somewhat controversial. Certainly if the onset is with shock, that should be treated first. As the bleeding

undoubtedly is diffuse and not focal in origin there is probably never an indication for thoracotomy and vessel ligation.

Aspiration is usually indicated after about 48 hours, as blood left in the pleural cavity may form fibrin clots, the latter requiring thoracotomy. The entire collection should be removed in one or two aspirations as the fewer the punctures the less danger there is of infection.

Replacement pneumothorax is probably of some value in certain cases to prevent a sudden change in intrapleural pressure. It is questionable if it is of any value in controlling bleeding, while it probably does increase the tendency toward pleural adhesions and its serious consequences.

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TREATMENT OF THE HYPERTENSIVE PATIENT IN THE PRE-CARDIAC STAGE

BY NATHAN FLAXMAN, M.D.

CLINICAL ASSOCIATE IN MEDICINE, IOIOLA UNIVERSITY MEDICAL SCHOOL, ASSOCIATE
ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL (SERVICE OF DR. HARRY J. LACROIX)
CHICAGO, ILLINOIS

At the present time there is only one treatment in the pre-cardiac stage of essential hypertension, and that is a rational medical management. How such treatment is effected and what constitutes a sensible management is an extremely debatable topic. One has only to review the literature on hypertension in the past two decades to find the truth of this statement.

My own views, tempered by the intensive experience of 10 years, are strongly conservative. Careful consideration needs to be given the hypertensive patient and his symptoms; he may require treatment for his "way of life" and for the alleviation of complications, such as obesity, nervousness and so on, rather than to reduce elevated blood pressure. I feel that nothing should be used when it makes the hypertensive patient more uncomfortable, such as the restriction of proteins or salt in his diet; that any drugs used should not have toxic manifestations, such as the sulfonylureas may produce; and that nothing should be employed which is time-consuming or expensive, such as so-called specific surgery. The hypertensive patient will sacrifice a great deal to obtain the therapy while imbued with hope for permanent relief, which does not exist at the present time. Essential hypertension is not an entirely hopeless disease, and the hypertensive patient should not and need not be unjustly inflicted with a constant fear for his life.

Principles of Treatment. Experienced practitioners have long recognized that drugs can reduce blood pressure, but only for short periods (Bishop²); that patients with high blood pressure might get better or worse according to what they were told of the figures, and that too

frequent blood pressure estimations might depress the patient (Potter³⁶); and that headaches and dizziness, supposed to be due to high blood pressure, may disappear with laxatives and diet and no change in blood pressure (Nicholson³¹).

From such writings the few well-established principles in the treatment of the hypertensive patient have developed: (1) the effects of drugs on the elevated blood pressure are transitory; (2) attention should be focused away from the blood pressure; and (3) the symptoms may be relieved by simple means without any change in the blood pressure.

A rational management may accomplish a great deal. In a small number of hypertensive patients the blood pressure may return to normal, and the symptoms disappear, permanently or for a prolonged period of time. Such remissions often recur spontaneously when the individual leads a well regulated life. In a somewhat larger number there is subjective improvement with some lowering of the blood pressure, although not to a normal level. In the largest group of hypertensive patients the blood pressure is not lowered much, if at all, but the symptoms are relieved and the patients are comfortable.^{43a}

Protein, Salt, and Fluid Consumption. Hypertensive patients are still seen who have been advised at one time or another not to eat red meat, or to use salt on their food, and to limit markedly the amount of fluids consumed daily. A few patients enjoy such a régime, for a while, as it gives them something that is different and temporarily adds interest to their presence among friends. The majority tires of the restrictions but are afraid to alter their diet unless assurance is given that such substances as red meat, salt, and fluids, in ordinary dietary amounts, have no effect on the labile blood pressure. One may safely give such assent to the hypertensive patient in the pre-cardiac stage, for it is definite that no relation exists between the use of protein,² salt,^{2,7,18,24,29,32} normal fluid intake,² and the elevation of the blood pressure. Robert,³⁷ who advocated the salt-free diet, cautioned that a rigid diet of this type, if protracted too long, may cause uremia.

Medicinals. A simple list of all the drugs employed in the treatment of essential hypertension is not only lengthy but confusing. A valuable contribution, which clarified the problem, was made by Ayman.^{3a} He showed that the symptoms associated with uncomplicated essential hypertension may be frequently relieved by the suggestion inherent in any seriously and enthusiastically prescribed drug or method of therapy.

Sulfocyanates. Sulfocyanates (thiocyanate) are probably the most widely advocated drugs for the treatment of hypertension. They^{19,30} were found to reduce the elevated blood pressure, and for a few years were used extensively. When untoward symptoms, ^{3b,34} such as marked weakness and angina pectoris, distressing side reactions, toxic manifestations, and death, occurred from its incautious use, the drug was dropped by many.^{4,15,23} Nobody should use it except in carefully selected occasional cases, and with the proper care to avoid harmful reactions. Sedatives, such as phenobarbital, relieve the symptoms

better than the sulfocyanates;¹⁷ but the latter causes a drop in blood pressure which is neither permanent nor necessarily desirable.

When Barker⁵⁴ introduced the method of controlling the dosage by the blood concentration, the use of the drug was revived. Barker and his co-workers⁴² have done good service by emphasizing the toxicity of the thiocyanates. They hope that their method of blood cyanate determinations will serve as a warning of the dangerous possibilities as well as a useful guide. Without such determinations they feel that the drug should not be used.

However, Garvin²¹ presented a case with fatal toxic manifestations which is significant in that the untoward symptoms occurred while the blood cyanates were at a supposedly non-toxic level. Russell and Stahl³⁹ reported a case in a hypertensive patient who had received only a total of 5.6 gm. of potassium thiocyanate over a period of 14 days. Robinson and O'Hare³⁸ treated 75 ambulatory hypertensives with potassium sulfocyanate and followed them closely by blood cyanate studies; toxic symptoms occurred in 29 (38%). In 23 of the 29 these consisted of nausea, weakness, dermatitis, purpura, and a decrease in libido. Serious complications consisting of dermatitis exfoliativa, congestive heart failure, cerebral thrombosis, angina pectoris, and psychoses occurred in 6 cases. In spite of such a large number of toxic manifestations, they concluded that this form of treatment in uncomplicated vascular hypertension in patients under 60 years of age, when carefully controlled, has decided value. Satisfactory results have been reported by Barker and his co-workers,⁵⁵ Blaney and his collaborators,¹⁰ Cannady and Allen,¹² Caviness and his associates,¹³ and Kurtz *et al.*²⁶

I myself have not used thiocyanate therapy to date in any hypertensive patient. My reasons are simple. When I began work in the out-patient dispensary of the Mt. Sinai Hospital, my colleague in the next room (Dr. Henry Siegel), who had preceded me there by 2 years, was employing the thiocyanates for such patients. Therefore, I decided to use only sedatives and to treat the hypertensive patient symptomatically. For the next 3 years, until he left the dispensary, we continued our separate therapies. On days that he was absent I saw his hypertensives, and *vice versa*. The only difference noted between the two groups was that mine were more comfortable, although his patients had a more pronounced lowering of blood pressure. True, the blood cyanate method was not used, but the length of time the patients were kept on the drug seemed sufficient to determine its value. The personal element could be excluded because of the same placid disposition in both, and we had plenty of time. After he left, I "inherited" his hypertensive patients, and thereafter followed all of them. As I could still see no real value to the thiocyanates, I do not use them in the treatment of the hypertensive patients.

Other Drugs. Liver extract^{14,27} was tried in the treatment of such cases, and discarded. I mention it only because an attempt is being made today to revive its use in hypertensives. Among the many other drugs which have been introduced, rapidly discarded, and reintro-

duced one or more times, are curcubocitrin (watermelon seed),^{1b,6,20} calcium lactate,¹⁴ magnesium sulphate by parenteral administration,⁴⁵ pancreatic extract,⁴⁴ bismuth subnitrate,^{3c,11,41} the nitrites,^{43b} iodides,¹⁶ xanthine and choline derivatives,¹⁶ hormones,^{3d} and garlic-parsley extracts. None of these drugs have any effect whatsoever on the relief of symptoms in the hypertensive patient other than that obtained by the temporary enthusiasm of the administrator.

Vitamin A. The last of the drugs introduced, although it is listed as a food and may be sold in grocery stores, is vitamin A.³⁵ To date not another reliable report on its use in hypertension has appeared; its value for this purpose remains to be demonstrated.⁸

Experimental Work. The last type of therapy suggested, *but not available*, is the use of parenteral extract of the whole normal kidney.^{33a} Because of the occasional shock-like reactions and the lack of standard chemical procedures to yield a uniform product of high potency, it cannot at present be regarded as a practical treatment.^{33b} In an extensive report Goldblatt, Kahn and Lewis²² stated that they tried on dogs with experimental renal hypertension a long list of substances which were used or are still being used in the treatment of human hypertension; and found that there was no significant effect on the blood pressure. Their results with renal extracts of other investigators, as well as with similar extracts of their own preparation, showed either no effect or at the most inconsistent and not very striking lowering of blood pressure in dogs with experimental renal hypertension.

Rational Therapy. How then, if all drugs mentioned have proven of no particular value, shall a hypertensive patient in the pre-cardiac stage be treated. By simply giving him a quiet, non-critical, sympathetic audience, the symptoms can at least be relieved.²⁸ It seems best not to make any reference to the degree of hypertension, its potential dangers, or its complications. The effect is not one of suggestion; for such patients encouragement about the reduction of the blood pressure is not necessarily good therapy. Many patients need only a good friend with whom they can discuss their troubles. Such difficulties may seem trivial, but are of importance to the patient. A little time, not much, and an unhurried physical examination each visit, with a critical eye on the size of the heart especially, are more assuring to a hypertensive than a non-effective drug.

The only non-toxic drugs, compared with the thiocyanates, used and advised for these patients are mild sedatives, such as phenobarbital and its derivatives in many forms, and a mild laxative such as cascara or rhubarb. By constant observation of many hypertensives I have found nothing as yet which indicates that such an extremely conservative type of optimistic therapy should be altered in the pre-cardiac stage. A sensible hypertensive patient can delay the appearance of the symptoms and signs of heart failure many years with the help of a good friend, his doctor. Symptomatic relief can be given to hypertensives by understanding them and treating them as individuals, rather than just as "cases" of hypertension to be treated by drugs which prove of little benefit.⁴⁰

Credo and Conclusions. When the unpreventable and unpredictable episodes of congestive heart failure, cerebral hemorrhage, coronary thrombosis, or uremia, occur in our hypertensive patients, we can only do our best, which may not be good enough at times. With proper understanding of the individual, we are getting hypertensive patients, except the uremics, back to health far more often than ever before, and with rational care they can and do live out their normal span of life despite the essential hypertension.

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RELATIONSHIP BETWEEN ARTERIOSCLEROSIS OF THE RENAL ARTERY AND HYPERTENSION

ANALYSIS OF 100 NECROPSIES

BY JAMES R. LISA, M.D.

PATHOLOGIST

DAVID ECKSTEIN, M.D.

RESIDENT PHYSICIAN

AND

CYRIL SOLOMON, M.D.

ASSISTANT VISITING PHYSICIAN

NEW YORK, N. Y.

(From the Pathological Laboratory and the First Medical Division, City Hospital, Welfare Island, Department of Hospitals)

EXPERIMENTALLY produced renal ischemia causes a hypertension in dogs and monkeys, which does not persist unless both main renal arteries are constricted. Since the original experimental work,⁵ case reports of so-called "Human Goldblatt Dogs" have been published by Leiter,⁷ Stewart,⁹ Freeman and Hartley,⁴ Blatt and Page,² Saphir and Ballinger,⁸ and others.

In an attempt to compare the experimental results with hypertension in the human, Blackman¹ examined the renal arteries of 50 hypertensive and 50 non-hypertensive individuals. He cut through the point of greatest narrowing after fixation, mounted and stained the sections and then measured the caliber. He found by this method that 86% of the hypertensive cases showed localized narrowing of the arteries varying from moderate to severe in degree of obstruction. Only 10% of the non-hypertensive cases showed partial obstruction. He concluded that the arteriosclerotic changes in the main renal arteries caused sufficient obstruction to induce chronic hypertension by the same mechanism as Goldblatt and others have shown to occur in animals. Blackman's findings have been accepted as explaining hypertension in humans with renal artery occlusion.

The present communication is a report of the condition of the main renal arteries in 100 consecutive cases coming to autopsy at this hospital in which blood pressure readings were obtained. No consistent correlation could be demonstrated between the condition or caliber of the main renal arteries and the presence or absence of hypertension.

The renal arteries attached to the segment of the aorta from which they arose were dissected free throughout their entire length and careful measurements of the arteries and all aberrant branches including the mouths were obtained with graduated sounds. Cross-sections of the vessels were made at the narrowest point. Where no perceptible narrowing existed, sections were taken 1 cm. from the mouth. The tissues were fixed in formalin, cut and stained with hematoxylin and eosin and an elastic tissue stain. The size of the arteries measured according to Blackman's method was compared with the size of the unfixed specimen obtained at the autopsy table. The kidneys were

studied histologically for the presence or absence of vascular changes compatible with hypertension. The hearts were examined histologically for the presence or absence of myocardial hypertrophy.

Among the 100 cases, 56 were hypertensive (31 men, 25 women), and 44 were non-hypertensive (27 men, 17 women). In the entire group there were 58 males and 42 females. The whites numbered 86, the negroes 14, approximately the relative ratio of admission of the two races to the hospital during the period in which this study was carried out. In the hypertensive group, 87.5% were white and 12.5% were black. The ages ranged from 17 to 87 years, the average was 60.3 years. The average age of the hypertensive group was 63.5 years and of the non-hypertensive 55.6 years. Of the 56 hypertensives, 47 were over 50 years of age.

No constant relation could be found between the size of normal non-sclerotic vessels as measured in the unfixed state and the size as found in the fixed stained specimen. Many which had a good caliber when examined at the autopsy table had a degree of contraction which would have justified their inclusion among those with a diminished caliber. Moreover the results were not uniform, so no accurate formula could be used. Because of these results, only the measurements obtained in the unfixed specimens were used for analysis.

Non-sclerotic vessels were regarded as normal. Among the hypertensive cases, 40% of the vessels were of this character. Among the non-hypertensive cases, the incidence was greater, 56.8%. The average diameter of the normal vessels was 4.1 mm. There was no significant difference in those of either group. With hypertension it was 4.1 mm.; with normal tension, 4 mm.

The average diameter of the vessels in all the cases of hypertension was 4 mm., practically the same as was found among the normal vessels in the group. There were only 2 instances of extreme stenosis of the renal arteries from sclerotic deposits simulating the Goldblatt dog. In the non-hypertensive cases, the average diameter of the entire group was also the same as in the non-sclerotic vessels, 4.1 mm. Although these vessels were slightly wider than among the hypertension group, there was no difference when the measurements were corrected for the age factor. Very little correlation between the amount of sclerosis and the degree of constriction of the lumen could be demonstrated. Linear sclerotic plaques caused practically no narrowing. In many instances the severely sclerotic vessels had lumens wider than normal. Although estimations of the cholesterol content of the vessels were not carried out, as was done by Bruger and Chassin,² our data suggest that the amount of cholesterol deposited in the vessel wall does not necessarily bear any relationship to its caliber.

The condition of the renal arterioles proved a more reliable guide to the level of the blood pressure reading than the caliber or condition of the extrinsic renal arteries. Goldblatt⁵ believed from his experimental work that renal ischemia from obstruction of the renal artery and its associated hemodynamic relationships produced hypertension. On the other hand, Page⁶ suggested that the lowering of pulse pressure

within the kidney itself was of more importance than a gross reduction of blood flow. The data obtained from the present study would tend to suppose the latter theory.

Summary and Conclusions. The caliber of the renal arteries was studied in 100 consecutive cases in which blood pressure readings were obtained. Hypertension was present in 56, normal pressures were found in 44. Marked variations were found in the caliber of non-sclerotic vessels when measured in the fresh state and in the fixed stained preparation, therefore, only the figures obtained in the fresh state were used for analysis. The differences of caliber between sclerotic vessels of the hypertensive and non-hypertensive cases were insignificant. Only two instances were found simulating the Goldblatt kidney. The degree of cholesterol deposit bore no relationship to the caliber. The degree and extent of arteriolar sclerosis estimated from the histologic examination of the kidneys proved a better index of the blood pressure readings than the caliber of the main renal arteries. The data lend more support to the theory advanced by Page than that of Goldblatt for the development of hypertension.

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THE SUBCUTANEOUS ADMINISTRATION OF SODIUM SULFATHIAZOLE IN VARIOUS CLINICAL CONDITIONS*

BY J. J. A. LYONS, M.D.

D. R. CLIMENKO, M.D., Ph.D.

AND

L. W. GORHAM, M.D.

ALBANY, N. Y.

(From the Departments of Medicine and Biochemistry, Albany Medical College)

The clinical efficacy of sulfathiazole in the treatment of certain infectious diseases is established beyond any doubt. The underlying principle of treatment with this drug, as with the other sulfonamides, is the establishment and the maintenance of an adequate concentration of the drug in the blood and the tissue fluids to control the rate of reproduction of the infecting organism. Ordinarily the oral administration of the drug is sufficient to attain and maintain such therapeutic

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blood levels. In certain acute, well-established infectious processes it is an accepted clinical practice to *attain* the therapeutic level rapidly by administering the drug intravenously, and to *maintain* this level by subsequent oral medication.

Occasions arise when the oral administration of the drug constitutes a serious practical difficulty in the clinical management of the patient, or becomes an actual impossibility. The usual procedure, when confronted with such a situation, is to administer the drug, in the form of its sodium salt, intravenously. A serious defect is associated with this approach, for under these circumstances a peak concentration is reached in the blood soon after administration is completed, which rapidly falls off as the drug is excreted. Thus, excessive concentrations are rapidly followed by ineffective levels, and therapeutic effectiveness is far from optimal. The intravenous route is admirable for rapidly disseminating the drug through the body, but it cannot be depended on as the sole method for the treatment of an acute infection.

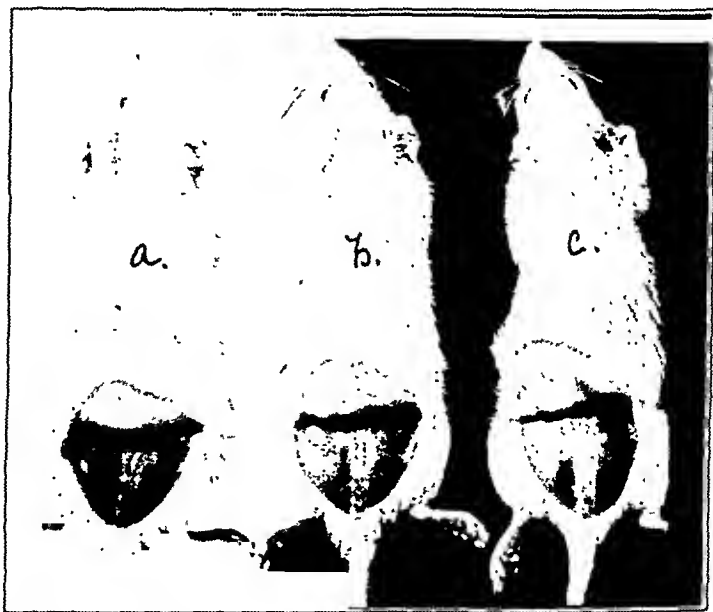


FIG. 1.—Subcutaneous reactions, 24 hours after the subcutaneous administration of 1%, 5%, and 10% aqueous solutions of sodium sulfathiazole. *a*, No reaction. *b*, Slight hyperemia in skin flap. *c*, Marked hyperemia with edema in skin flap.

Some time ago Finland and his co-workers³ using the water-soluble glucose addition product of sulfapyridine, showed that this compound might be administered subcutaneously without fear of local reactions. Unfortunately, they also pointed out that the glucoside was relatively inert from a therapeutic point of view.⁴ Flippin¹ has dealt with the problem by advocating the intramuscular administration of concentrated (33%) solutions of the sodium salt of sulfapyridine.

The pharmacologic evidence presented by Powell and Chen⁵ and

by Marshall⁶ indicated that the alkaline aqueous solutions of the sodium salts of drugs like sulfapyridine are extremely irritating and that the subcutaneous administration of such solutions might cause severe local reactions or actual tissue destruction. We have found this to be true when concentrations of the order of 10% or higher are administered subcutaneously to experimental animals. We have also observed that such experimental animals tolerate the subcutaneous administration of 1% aqueous solutions of the anhydrous sodium salt of sulfathiazole without showing any sign of tissue reaction, and that only a transient hyperemia results from the subcutaneous administration of a 5% solution.

Figure 1 shows the local reactions in a series of rats to the subcutaneous administration of 0.5 cc. of a 1%, 5%, and 10% solution of sodium sulfathiazole, 24 hours after medication. Animals receiving the 1% solution showed no reaction whatsoever; those receiving the 5% solution showed a slight degree of hyperemia at the end of 24 hours which had practically disappeared at the end of 48 hours, and left no trace whatsoever by the end of 72 hours. The animals receiving the 10% solution showed marked hyperemia and edema at the end of 24 hours which persisted. The lesion became indurated, and involved the subtending fascia by the 72d hour.

Aqueous solutions of the anhydrous sodium salt of sulfathiazole have the following physical properties:

TABLE 1.—PHYSICAL PROPERTIES OF AQUEOUS SOLUTIONS OF SODIUM SULFATHIAZOLE

Concentration	pH	Freezing point depression
0.5	9.55	0.07
1.0	9.72	0.14
5.0	9.8-10.0	0.605
10.0	10.0-10.2	(crystallizes out in cold)
25.0	10.39	

Thus, even 1% solutions are definitely hypotonic; such solutions may be brought to isotonicity by the addition of 0.62% of NaCl. In practice we have neglected this factor and used the hypotonic solutions for subcutaneous injection.

Our clinical evidence agrees with the observations of Taplin and his co-workers⁷ and bears out our experimental findings. Up to the present time, more than 200 individuals in the Medical, Gynecological and Surgical Services of the Albany Hospital have received up to 2000 cc. of a 0.5% aqueous solution of sodium sulfathiazole per day, administered subcutaneously at a rate of approximately 100 cc. per hour, without showing a single, serious untoward local reaction. The most serious local reaction encountered in this group of patients was a slight swelling and tenderness of the injection site, which cleared up within a few hours after the application of a hot water bottle. This occurred in 8 patients in our entire series.

The group included all ages: the youngest patient being an infant of 3 weeks suffering from lobar pneumonia, the oldest a man aged 82 suffering from an acute infection of the urinary tract. Figure 2 shows the age distribution of the group.

Sexes were represented almost evenly: 55% females, 45% males. The clinical conditions treated by this method included the usual variety of pathologic states which have shown themselves to be amenable to therapy with this drug, but where oral administration of the drug was either contraindicated or impossible.

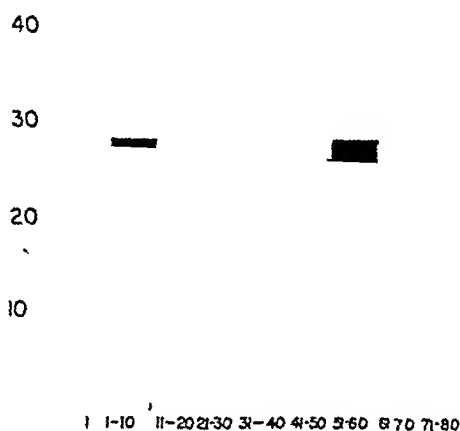


FIG 2.—Age distribution of patients medicated with subcutaneously administered sodium sulfathiazole

The following table gives a summary of the clinical results:

TABLE 2 —A SUMMARY OF THE CLINICAL RESULTS

Clinical entities	Total No of cases	Results	
		Recovered	Died
Acute appendicitis with peritonitis	54	53	1
Pelvic peritonitis	31	31	0
Postoperative hyperpyrexia	25	24	1
Intracranial infections	15	11	4
Postoperative pneumonia	11	11	0
Postoperative peritonitis	11	7	4
Ruptured ulcer with peritonitis	5	3	2
Laryngo-tracheobronchitis	1	0	1
Postoperative urinary tract infections	3	2	1
Lobar pneumonia (complicated)	12	8	4
Puerperal sepsis (including septic abortions)	10	10	0
Post-traumatic infections	6	3	3
Miscellaneous	10	9	1

Infecting organisms included: *Staph. aureus*, *Staph. albus*, Hemolytic streptococcus, non-hemolytic streptococcus, *Strep. viridans*, *B. coli*, *H. influenzae*, Pneumococci, Types I, II, III, VI, XII, XIII, XV, XIX, XXI, XXII, XXIII, XXV, XXVII, XXIX, XXXII.

Blood concentrations of the drug following this type of medication are somewhat lower than would be expected if the same quantity of the drug had been administered orally. No adequate explanation can be given for this observation at the present time; it may be due to the fact that these individuals were receiving large quantities of parenteral fluids, which would tend to speed up the passage of the drug through the body. This suggestion is substantiated by the small proportion of

acetylated drug which is present in the blood under these circumstances. Following oral administration from 10% to 20% of the drug in the blood is conjugated, while only 5% to 10% is conjugated following subcutaneous administration.

Figure 3 shows the maximum blood concentrations obtained after the subcutaneous administration of 5 gm. of the sodium salt of sulfathiazole in a 12-hour period.

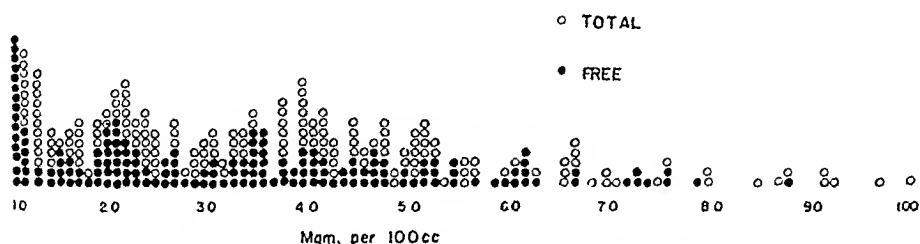


FIG. 3.—Maximum blood concentrations following the subcutaneous administration of 5 gm. of sodium sulfathiazole in 12 hours.

Two cases of complete anuria occurred; both recovered following catheterization of the ureters and the intravenous administration of slightly alkaline buffers. Frank hematuria occurred in 4 instances, while 30 patients showed microscopic crystalluria or occult hematuria. Three patients showed mild secondary anemia.

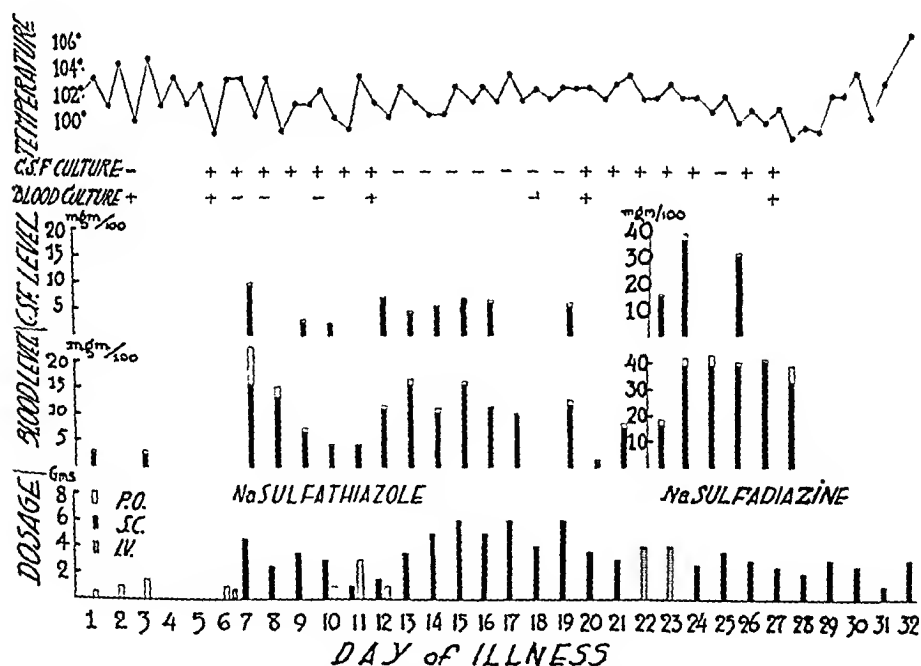


FIG. 4.—A fatal case of *H. influenza* meningitis in an infant. The chart shows, from above down: temperature, cerebrospinal fluid culture, blood culture, cerebrospinal fluid drug content, blood drug content, and dosage.

The incidence of toxic reactions to medication is somewhat higher than would be expected. It should be pointed out, however, that the patients comprising this clinical group were acutely ill; 75% of them had undergone recent major surgical intervention.

Figure 4 diagrammatically illustrates the clinical course of a fatal case of *H. influenzae meningitis* in an infant. This case is presented in order to demonstrate the blood and cerebrospinal fluid levels attained as a result of the oral, subcutaneous and intravenous administration of sodium sulfathiazole or sodium sulfadiazine. During the early stage of the illness, the administration of the drug was by gavage, but the intestinal distention which resulted from this method of administration made it necessary to resort to some other means of medication. The subcutaneous route was chosen.

During the course of this investigation, sodium sulfadiazine was made available to us. On experimental animals it appeared to be slightly more irritating than the sodium salt of sulfathiazole. However, the administration of equal quantities showed that the sulfadiazine salt gave rise to much higher blood concentrations than did the sulfathiazole salt; this, together with the fact that sulfadiazine traversed the cerebrospinal barrier more readily than does sulfathiazole, led us to try sodium sulfadiazine in the treatment of a number of cases of meningitis. No local reactions were observed. One such case is illustrated where both sodium salts of sulfathiazole and sulfadiazine were employed. In neither instance was there any irritative reaction.

More recently, Jorgensen and Greeley² reported on the administration by hypodermoclysis of $\frac{1}{2}$ to 1% solution of sodium sulfadiazine to infants without resulting in a single local reaction. They have used repeated subcutaneous injections of solutions up to 5% without any deleterious reactions.

The chart in Figure 4 illustrates two points to which attention has already been called: (1) Higher blood levels are attained after the administration of sulfadiazine than result from the administration of comparable doses of sulfathiazole. (2) Cerebrospinal fluid concentrations of the drug are much greater after sulfadiazine than they are after sulfathiazole.

Conclusion. The subcutaneous administration of dilute (0.5%) solutions of sodium sulfathiazole afford a safe, practical method for the administration of this drug when oral administration is contraindicated. This conclusion is based upon a study of the physical properties of dilute solutions of sodium sulfathiazole, upon the administration of such solutions to experimental animals, and upon a clinical study of 200 patients who have received sodium sulfathiazole by the subcutaneous route.

The anhydrous sodium sulfathiazole used in this study supplied by Winthrop Chemical Company, New York, N. Y.

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THE THERAPY OF EXPERIMENTALLY INDUCED GANGRENE

PART I. A METHOD OF TESTING LOCAL ANTISEPTICS IN VIVO

BY KARL K. GRUBAUGH, M.A.*

AND

WILLIAM A. STARIN, PH.D.

COLUMBUS, OHIO

(From the Department of Bacteriology, The Ohio State University)

THE primary object of this study was the elaboration of a method for the study of antiseptic action that was based upon *in vivo* experiments. We selected Azochloramid as a presumably effective and safe compound on the basis of many reports which compare its effectiveness with that of other antiseptics, both in bactericidal tests, and in determinations of toxicity (chemotherapeutic) indices.^{6,9,10,13}

The development of a technique of producing and treating controlled wound infection in experimental animals has been the goal of many investigations since none of the *in vitro* methods used for the evaluation of local antiseptics permit prediction of their effect in the treatment of wounds.

However, as shown by Reinhardt, Scheimann *et al.* (as described by Browning²), also by Kroll *et al.*⁸ experimental wounds infected with streptococci either heal spontaneously in a short time, or the infection is so overwhelming that death of the animal is quickly brought about by a septicemia which obviously could not yield to local treatment. Hertz and Hunt^{5,7} used *S. aureus* to produce abscesses in mice and hamsters. Healing occurred without treatment in 7 to 8 days; thus the effect of the treatment could not be easily determined.

Somewhat more promising results were obtained when the experimental wound infection was brought about by the use of anaërobic spore-forming organisms. This is largely due to the fact that the infection takes a course slow enough so that an efficient local antiseptic might influence it, and due to the fact that if left untreated, it usually ends fatally, providing an end-point for the control animals. This experimental approach was successfully used by Bliss, Long and Smith.¹

Since experimental wounds infected with anaërobic bacteria are usually deep and develop tissue necrosis, the treatment requires disinfectants which have penetrating power and activity in the presence of slough and débris. We, therefore, undertook to examine the use of experimentally infected wounds in evaluating a local antiseptic *in vivo*.

Experimental Procedure. Stock cultures of *Clostridium histolyticum*, *Cl. perfringens* and *Cl. septique* were grown in a medium consisting of a veal infusion broth containing 1% proteose peptone, 0.25% dextrose and 1% tryptophane, adjusted to a pH of 7.6. The medium was distributed into large test tubes into which 2 to 3 gm. of finely chopped meat had been placed, which aided in the reduction of the oxygen

* Present address Research Laboratories, Wallace & Tiernan Products, Inc., Belleville, N. J.

tension of the medium, and furnished additional material for growth. After boiling for 5 minutes to drive out the oxygen and cooling quickly afterwards to prevent reabsorption, the medium was inoculated with 0.5 cc. of the bacterial suspension and sealed with a layer of sterile petrolatum. This method was found to be satisfactory for producing the anaërobic conditions required by the organisms.

The Azochloramid solution used throughout the work was prepared by dissolving 9.45 gm. of the commercially available Azochloramid-salt mixture in 1000 cc. of warm distilled water. The resulting isotonic saline solution contained Azochloramid in a concentration of 1:3300 and was buffered at pH 7.4. The exact concentration of Azochloramid was checked by iodometric titration.

Guinea pigs of approximately the same size, weighing on an average 600 gm. and Syrian hamsters averaging about 120 gm. were used for the experiments. Wounds were produced in the following manner: The animals were anesthetized by injecting 0.3 cc. of nembutal intraperitoneally. The hair of the leg and back was removed by clipping, the thigh washed with alcohol and the skin and muscle of the thigh were then bruised by pinching with a heavy sterile forceps. This resulted in the formation of a slightly edematous contused area of about 0.5 cm. in diameter. Care was taken not to break the skin. The infection was produced by immediately injecting into this bruised area 0.5 cc. of a broth culture of *Cl. histolyticum*, or of a mixture of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septicus* cultures. In order to preclude too rapid development of an overwhelming infection, the injection was made superficially. When the culture of a single organism was injected the infections were well established after 15 to 20 hours. They were characterized by marked swelling and stiffening of the leg, lysis, destruction and sloughing of the skin over the area of the wound, which, at this stage, had increased to about 2.5 cm. in diameter. The muscles were pale pink in color. In other groups of animals the gangrenous lesions were produced by inoculating with 0.5 cc. of a mixed culture of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septicus*. The lesions were of similar appearance as the ones produced by *Cl. histolyticum* alone but appeared sooner, approximately 10 hours following the infection.

In the control animals the lesions continued to increase in extent until the whole lower leg became involved. In most cases these animals died on the 3d or 4th day due to invasion of the abdominal cavity followed by peritonitis. In some instances, this was preceded by complete destruction and lysis of the tissue of the leg and thigh, leaving the bone exposed.

In the test animals, treatment with the antiseptic was instituted 15 to 20 hours after the injection of the single culture, or 10 hours after the injection of a mixed culture, when active lesions showing necrosis and edema had been well established. The animals were anesthetized with nembutal. The wound area was irrigated and washed with cotton swabs saturated with the aqueous solution of Azochloramid. After the wounds were cleaned a wet dressing con-

sisting of a pledget of cotton saturated with the Azochloramid solution was applied in such a way that good contact was maintained with all parts of the affected region. No attempt was made to bandage the leg with gauze or tape as the animals have a tendency to tear at them until they come off and, in so doing, might enlarge or contaminate the lesions with other organisms. The wet dressing was allowed to stay in contact with the wound for as long a period as the anesthetic kept the animal quiet, usually several hours.

This treatment was carried out twice daily for 3 to 4 days, during which time a heavy scab formed over the wound. Following this, the applications of Azochloramid were reduced to one a day for 3 to 4 days; then the wound was allowed to heal without further attention. Usually, the first scar and large amounts of dead tissue had sloughed off within 14 days, a thinner, lighter colored scab having formed beneath. In most cases, complete recovery occurred in about a month with only a small scar remaining. (Table 1.)

In some of these experimental infections in guinea pigs it was also decided to test the effect of a wetting agent, sodium tetradecyl sulfate (sodium 2-methyl 7-ethyl undecanol-4 sulfate) along with Azochloramid. The difference in the time of healing of the wounds does not seem to be significant (Table 1).

TABLE 1.—EFFECT OF TREATMENT WITH AZOCHLORAMID ON EXPERIMENTALLY INFECTED WOUNDS IN GUINEA PIGS

Infections	Treatment	Animals, No.	Recovered	Deaths	Recovered, %
<i>Cl. histolyticum</i> . .	None	7	1	6	14
<i>Cl. histolyticum</i> . .	Azochloramid	22	20	2	91
<i>Cl. histolyticum</i> *	None	11	1	10	9
	Azochloramid	21	15	6	71
<i>Cl. perfringens</i> *	Azochloramid and wetting agent	9	8	1	89
<i>Cl. septicus</i> *		5	1	4	20

* Mixed culture.

Experimental infections were also produced in Syrian hamsters. In view of the smaller size of these animals, the amount of bacterial suspension injected was reduced to 0.2 cc. Typical lesions described above were produced in 15 to 20 hours and the treatment was carried out in the same manner and to the same extent as with the guinea pigs.

A group of hamsters was infected with the mixed culture of organisms and, although the lesions developed more rapidly, the severity of the acute infection was overcome in about 8 to 10 days. The wounds healed completely in about 3 weeks leaving only a small scar (Table 2).

TABLE 2.—EFFECT OF TREATMENT WITH AZOCHLORAMID OF EXPERIMENTALLY INFECTED WOUNDS IN SYRIAN HAMSTERS

Infection	Treatment	Animals, No.	Recovered	Deaths	Recovered, %
<i>Cl. histolyticum</i> . .	Azochloramid	13	11	2	85
<i>Cl. histolyticum</i> . .	None	5	1	4	20
<i>Cl. histolyticum</i> *	Azochloramid	10	9	1	90
<i>Cl. perfringens</i> *		5	0	5	0
<i>Cl. septicus</i> *	None				

* Mixed culture.

Controls were used with each group of animals undergoing treatment. These controls were infected in the manner described, some received no treatment whatever, while others were treated with sterile saline following the procedure outlined for Azochloramid in the test animals. The saline treatment had no effect on the course of the infection.

During the course of treatment of the infected wounds of both guinea pigs and hamsters, the types of organisms present were studied by making smears of some of the edematous material of each lesion at 2-day intervals. Following 4 to 6 days' treatment the organisms had disappeared from the wounds. In several animals staphylococci were found, but none were seen in stained preparations from the lesions of treated animals made 1 or 2 days after their appearance if treatment was continued.

Conclusions (Part I). Experimentally induced gangrene was produced in guinea pigs and Syrian hamsters either with *Cl. histolyticum* or with mixtures of cultures of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septicus*. The infections in the test animals were treated with a stock solution of Azochloramid or with Azochloramid combined with a wetting agent, sodium tetradecyl sulfate. Of this group there were 71 to 91% recoveries as compared with an 80 to 100% mortality in the control animals. In these experiments there was no significant difference between the action of Azochloramid itself and that containing a wetting agent; each gave good results when used in treatment of the gangrenous lesions in guinea pigs.

The results of the experiments demonstrate the marked effect of Azochloramid when used as a therapeutic agent on gangrenous wounds in animals. The severity of the infections with *Cl. histolyticum* was quickly reduced by daily treatments with Azochloramid for a period of 10 days, and complete healing of the wounds in both guinea pigs and hamsters resulted within 1 month. Similar results were obtained in the treatment with Azochloramid of experimentally induced wounds with mixed cultures of *Cl. perfringens*, *Cl. histolyticum* and *Cl. septicus*.

These therapeutic effects are undoubtedly due to the ability of Azochloramid to destroy and inactivate the toxins and lysins of these anaerobes in concentrations far below those required to inhibit growth.

PART II. THE EFFECT OF AZOCHLORAMID ON VARIOUS ANAEROBIC BACTERIA AND THEIR TOXINS

Anaerobic bacteria, common inhabitants of the soil, are not infrequently encountered in traumatic and war wounds. Although they have little invasive ability, their toxins damage the surface tissue by destruction and lysis. Of this group of anaerobic bacteria those associated with gas gangrene, botulism and tetanus are the most important.

The effect of an antiseptic on the growth, hemolysins and lethal toxins of this group of bacteria was considered of interest. An investigation was made to determine the efficacy of Azochloramid (N,N'-

Dichloroazodicarbonamidine),¹¹ a chlorine compound deriving its bactericidal effect from the slow release of hypochlorous acid in a water solution. Its advantage over other chlorine compounds lies in its stability in the presence of extraneous organic matter. Guiteras and Schmelkes³ have shown that Azochloramid reacts with amino acids and proteins only to a slight extent under conditions where the other chlorine compounds are easily inactivated.

Since this work was started, Heise and Starin⁴ have reported similar studies with staphylococci.

Experimental Procedure. The organisms used in these studies were 3 strains of *Cl. perfringens*, and 1 strain each of *Cl. histolyticum*, *Cl. tetani*, *Cl. botulinum* and *Cl. septicum*.

The medium for culture and toxin production of these organisms is the same as that described in Part I. The crude toxins used in all tests were obtained by filtering the broth cultures through Berkefeld "V" candles.

For the tests to determine the inhibiting power of Azochloramid on growth and toxin production of these organisms, solutions of Azochloramid were added directly to the culture tubes so that each tube contained a definite concentration ranging from 1:3300 to 1:33,000. The tubes were then inoculated with 0.5 cc. of a heavy suspension of the organism, immediately sealed with sterile petrolatum, and incubated for 24 hours at 37.5° C. Growth was determined by the turbidity of the culture tubes after 24 hours and subcultures were made for confirmation.

The presence of hemolysins was determined by filtering the 24-hour broth cultures through Berkefeld "V" candles and using this filtrate as follows:

Red blood cells obtained from horse, sheep, rabbit and human blood were centrifuged and washed 3 times with physiologic saline solution. A 3% cell suspension was then made up in saline buffered at a pH of 7.4. One cc. quantities of the filtrate were distributed in small test tubes; 0.5 cc. of the 3% cell suspension was added to each tube, and the volumes were brought to 2.5 cc. with buffered saline. The tubes were well shaken and incubated in a water-bath for $\frac{1}{2}$ hour at 37.5° C. The final results were read after storing the tubes in a cold room for 24 hours.

The presence of lethal toxins in the filtrates from the cultures which grew in the presence of Azochloramid was determined by intravenous injection of 0.2 cc. of the filtrate into mice. The mice used were of a standard age of 12 weeks.

The effect of Azochloramid on preformed hemolysins produced by the various groups of anaërobes when grown under optimum conditions were studied. The organisms were grown until the maximum quantity of hemolysins was obtained. The filtrates from these broth cultures were titrated with erythrocytes to determine the concentration of hemolysin produced by each organism. The highest dilution of hemolysin producing 50% hemolysis was taken to be the minimal hemolytic dose (m.h.d.).

Multiple series of dilutions of Azochloramid-salt mixture were prepared. To each series was added 1 cc. amounts of each filtrate containing known multiple m.l.d. The tubes were well shaken, then incubated in a water-bath for $\frac{1}{2}$ hour at 37.5° C. At the end of this time 0.5 cc. of a 3% suspension of red cells was added to each tube and they were again shaken and incubated for $\frac{1}{2}$ hour. The tubes were placed in the cold room and a final reading for hemolysis was made after 24 hours.

A study was made of the action of Azochloramid on the lethal toxins as produced by the organisms in artificial culture medium under optimum conditions. The minimal lethal dose (m.l.d.) for mice of the toxic filtrates of the different organisms was carefully determined. One m.l.d. for mice was the amount of toxin that would kill mice of standard size and age in 24 hours when injected intravenously. The effect of Azochloramid on these toxins was determined by mixing 1 cc. amounts of toxin containing multiple m.l.d. with Azochloramid. Each tube containing these mixtures was well shaken and placed in a water-bath for $\frac{1}{2}$ hour at 37.5° C., after which 0.2 cc. of each toxin-Azochloramid mixture was injected intravenously into mice.

Complete protection of the treated animal was the arbitrarily selected criterion of the inhibitory potency of Azochloramid against the lethal toxin. The protective value was expressed in terms of the amount of Azochloramid that would protect the mouse against the multiple m.l.d. injected. As the toxin of *Cl. botulinum* is so much more potent than those of the other anaerobes studied, a special test was carried out with it as follows: 1 cc. amounts of the stock Azochloramid-salt solution (1:3300) were added to 1 cc. of diluted toxin. These dilutions contained between 100 to 4000 m.l.d. The tubes were well shaken, then incubated in a water-bath for $\frac{1}{2}$ hour at 37.5° C. Following this 0.4 cc. of each mixture was injected intravenously into mice.

Results. The results obtained when Azochloramid is incorporated in the culture medium are indicative of its inhibiting action on the growth of the different bacterial species. The concentration of Azochloramid necessary to cause complete inhibition of growth varies; i. e., *Cl. perfringens* was completely inhibited by a dilution of 1/5280; *Cl. histolyticum* by 1/6600; *Cl. tetani* by 1/8250; *Cl. botulinum* by 1/4720, and *Cl. septicum* by 1/5280. These are the minimum concentrations preventing growth in the culture tubes. Such negative observations were always confirmed by subcultures (Table 3).

The development of hemolysins for different types of erythrocytes was also inhibited by Azochloramid in the medium (Table 3). This reaction was prevented by lower concentrations of Azochloramid than those required to prevent growth. Effective concentrations range between 1/5280 for *Cl. botulinum* to 1/8250 for the other anaerobes studied. No variation was noted with respect to the inhibition of the hemolysins for the erythrocytes of the different species.

The production of lethal toxin was similarly inhibited by the presence of Azochloramid in the culture medium. Examination of the data in Table 3 shows that in most instances inhibition of formation of the

lethal toxins is brought about with even lower concentrations of Azochloramid than inactivation of hemolysins. Effective concentrations range between 1/8250 for *Cl. histolyticum* to between 1/16,500 and 1/33,000 for the various strains of *Cl. perfringens*.

TABLE 3.—THE INHIBITION OF HEMOLYSIN, LETHAL TOXIN AND GROWTH WHEN AZOCHLORAMID WAS INCORPORATED IN THE CULTURE MEDIUM

Organism	Strain	Dil. of Azochloramid in medium preventing					
		Hemolysin production				Lethal toxin production	Growth
		Horse	Sheep	Rabbit	Human		
<i>Cl. perfringens</i>	O.S.B.H.	1:8250	1:8250	1:8250	1:8250	1:33,000	1: 5,280
<i>Cl. perfringens</i>	Hall	1:8250	1:8250	1:8250	1:8250	1:16,500	1: 5,280
<i>Cl. perfringens</i>	Novy	1:33,000	1:10,890
<i>Cl. histolyticum</i>	Spray	1:8250	1:8250	1:8250	1:8250	1: 8,250	1: 6,600
<i>Cl. tetani</i>	O.S.U.	1:8250	1:8250	1:8250	1:8250	.	1: 8,250
<i>Cl. botulinum</i>	M ₇ A ₂	1:5280	1:5280	1:5280	1:5280	*	1: 4,720
<i>Cl. septicum</i>	O.S.U.	1:8250	1:8250	1:8250	1:8250	1:16,500	1: 5,280

* Where growth occurred when *Cl. botulinum* was cultured in the presence of Azochloramid a lethal toxin could always be demonstrated.

The hemolysins used in this study were produced by growing the organisms under anaërobic conditions in the artificial medium previously described for the time required to produce the maximum yield. The results indicate that Azochloramid has a marked effect on hemolysins even in low concentrations. As a uniform volume of filtrate was used throughout the experiment and the potency of the hemolysin for the different organisms varied between 10 m.h.d. and 20 m.h.d. per cc. the concentration of Azochloramid necessary to inactivate the different hemolysins was not strictly comparable. The concentrations of Azochloramid capable of reducing the hemolytic titres are quite low, ranging between 1/16,500 and 1/33,000 when tested against multiple m.h.d. (Table 4).

TABLE 4.—THE EFFECT OF AZOCHLORAMID ON THE HEMOLYSINS OF VARIOUS ANAEROBIC BACTERIA

Organism	Strain	No. of m.h.d. in 1 cc.	Dil. of Azochloramid which completely inhibits the lysis of cells			
			Horse	Human	Sheep	Rabbit
<i>Cl. perfringens</i>	O.S.B.H.	20	1:26,400	1:26,400	1:26,400	1:26,400
<i>Cl. perfringens</i>	Hall	20	1:26,400	1:26,400	1:26,400	1:26,400
<i>Cl. histolyticum</i>	Spray	10	1:33,000	1:26,400	1:33,000	1:26,400
<i>Cl. tetani</i>	O.S.U.	10	1:26,400	1:33,000	1:26,400	1:26,400
<i>Cl. botulinum</i>	M ₇ A ₂	8	1:33,000	1:33,000	1:33,000	1:33,000
<i>Cl. septicum</i>	O.S.U.	15	1:16,500	1:16,500	1:16,500	1:16,500

The preformed lethal toxins used in this investigation were produced by growing the various anaërobic organisms under optimum conditions for the length of time necessary for the production of a maximum yield of potent toxin. The results of these experiments demonstrate the marked effect of low concentrations of Azochloramid on the lethal toxins of the organisms studied. The amount of lethal toxin used varied with the different organisms since a constant volume of toxic filtrates was used throughout these experiments. The titres of different toxins varied from 8 m.l.d. for *Cl. perfringens* (Novy strain) to 100,000 m.l.d. per cc. for *Cl. botulinum*. Therefore, again the minimum inhibiting concentrations of Azochloramid are not strictly comparable.

The protective value of Azochloramid was defined as that amount which would react with the toxin in such a way as to render it inactive when multiple m.l.d. were injected into the mice. The results show, as may be seen in Table 5, that low concentrations of Azochloramid have the capacity to inactivate the lethal toxins even when multiple m.l.d. are injected. The dilutions of Azochloramid inactivating these toxins ranged from 1/16,500 for the 3 strains of *Cl. perfringens* and *Cl. septicum* to 1/33,000 for *Cl. histolyticum*. The m.l.d. per cc. of the lethal toxins varied a great deal but the same high dilution of Azochloramid had an equal effect on the multiple m.l.d. of each toxin. The toxin of *Cl. botulinum* was an exception in this test when the same procedure was followed as with the other toxins. When 1 volume of this toxin containing 100,000 m.l.d. was mixed with an equal volume of a standard saline solution of Azochloramid (1:3300) the toxic filtrate was not inactivated as the injected mice died in the same time as the controls.

TABLE 5.—THE EFFECT OF AZOCHLORAMID ON THE LETHAL TOXINS OF VARIOUS ANAEROBIC ORGANISMS

Organisms	Strain	No. of m.l.d. in 1 cc.	Dil. of Azochloramid that protected mice from multiple m.l.d. of toxin
<i>Cl. perfringens</i>	O S B.H	15	1:16,500
<i>Cl. perfringens</i>	Hall	20	1:16,500
<i>Cl. perfringens</i>	Novy	8	1:16,500
<i>Cl. histolyticum</i>	Spray	20	1:33,000
<i>Cl. botulinum</i>	M ₇ A ₂	100,000	No protection
<i>Cl. septicum</i>	O S U.	17	1:16,500

Therefore, a special experiment was set up to determine the largest number of m.l.d. against which the stock solution of Azochloramid was effective. The results of this test, as seen in Table 6, show that a dilution of 1/3300 of Azochloramid will protect mice against a maximum of 250 m.l.d. of the *Cl. botulinum* toxin.

TABLE 6.—THE EFFECT OF AZOCHLORAMID ON *Cl. BOTULINUM* TOXIN

M.l.d.	Amt. toxin	Azo (1/3300)	Incub.	Amt. inject	Survival time (in days)				
					1	2	3	4	5
100	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	+	+	+	+	+
250	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	+	+	+	+	+
500	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.4 cc.	+	—	—	—	—
750	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	—	—	—	—	—
1000	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	—	—	—	—	—
1500	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	—	—	—	—	—
2000	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	—	—	—	—	—
4000	1 cc.	1 cc.	$\frac{1}{2}$ hr. 37.5° C.	0.1 cc.	—	—	—	—	—

+ = living, — = died, * = complete protection

Conclusions (Part II) 1. Low concentrations of Azochloramid (1/1720 to 1/10,980) when incorporated in the culture medium inhibit the growth of various groups of anaerobic bacteria.

2. The production of hemolysins and lethal toxins of these organisms in the culture medium is inhibited by even lower concentrations of Azochloramid (1/5280 to 1/33,000).

3. When acting upon filtrates of these organisms, similarly low con-

centrations of Azochloramid inactivate appreciable amounts of pre-formed hemolysins and lethal toxins.

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STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERIZINE, SULFAMETHYLDIAZINE) IN MAN*

I. ABSORPTION, DISTRIBUTION, AND EXCRETION

By FRANKLIN D. MURPHY, M.D.

GODEY AND SEEGER FELLOW IN MEDICINE, UNIVERSITY OF PENNSYLVANIA

JOHN K. CLARK, M.D.

EDWARD BOK FELLOW IN MEDICINE, UNIVERSITY OF PENNSYLVANIA

AND

HARRISON F. FLIPPIN, M.D.

ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA

PHILADELPHIA, PA.

With the Technical Assistance of ELIZABETH PATCH, A.B.

(From the Department of Medicine and the William Pepper Laboratory of the Hospital of the University of Pennsylvania)

THE disadvantages associated with the sulfonamide drugs now in common use have led to an increasing search for an improved derivative. In an attempt to find a more satisfactory sulfonamide, we have interested ourselves in sulfamerizine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine), the methyl homologue of sulfadiazine, which has been synthesized by several groups of investigators.^{2,6,7} The therapeutic activity of sulfamerizine was described by Roblin *et al.*⁶ at the same time that they reported on sulfadiazine and it was shown that in preliminary mouse tests both of these drugs were considerably more active against streptococcal, pneumococcal, and staphylococcal infections in mice than sulfanilamide, sulfapyridine, or sulfathiazole. Pharmacologic studies in various species of laboratory ani-

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mals,⁸ and humans^{3,8} have indicated that sulfamerizine is more rapidly and more completely absorbed from the gastro-intestinal tract than sulfadiazine. Furthermore, it was shown by Weleli *et al.*⁸ that sulfamerizine and its acetyl derivative were more soluble in urine than sulfadiazine and acetylsulfadiazine. Further studies by this group⁸ suggested that sulfamerizine is no more toxic in experimental animals than sulfadiazine when a comparison is made on the basis of blood concentration of the drugs.

The present report offers certain observations dealing with the absorption, distribution, and excretion of sulfamerizine* in humans. Two groups of experiments were conducted, those in which a single dose of the drug was administered orally, subcutaneously, intravenously, or rectally, and those in which multiple doses were administered over a period of days.

Methods and Materials. Sulfamerizine was determined by the method of Bratton and Marshall¹ with the exception that para-toluene-sulfonic acid was used as protein precipitant for most of the work in place of trichloroacetic acid. Studies on acetylated sulfamerizine in blood have shown that from 5% of the drug at low concentrations to 15% at higher concentrations is not recovered by this method and we have corrected our results accordingly; the slight loss may be due to adsorption of the drug during blood protein precipitation. Determinations of sulfamerizine were made on serum because of the variability in the amount of drug found in the red blood cells when whole blood is used. The fate of a single dose of sulfamerizine, administered by various routes, was studied in 16 patients who were selected on the basis of normal gastro-intestinal, hepatic, and renal function and were for the most part young healthy males convalescing from minor surgical procedures. No attempt was made to determine the exact fluid intake but it approximated 1500 to 2000 cc. in 24 hours. The 21 patients in whom body fluid concentrations were studied fell into no specific category and varied from healthy to seriously ill individuals. Continuous administration of sulfamerizine was studied in 15 patients suffering from a variety of diseases, including pneumococcal pneumonia, meningococcal meningitis, hemolytic streptococcal cellulitis and subacute bacterial endocarditis.

Results. A. ABSORPTION AND EXCRETION OF SULFAMERIZINE. 1. *Fate of a Single Oral Dose* (Table 1). Eight (Nos. 1, 2, 3, 4, 5, 6, 7, and 8) young male patients were given 3 gm. of sulfamerizine by mouth. Blood specimens were taken at appropriate intervals and urine collected over 24- and 48-hour periods. At the end of 2 hours the average concentration of free sulfamerizine in the serum was 12.8 mg. per 100 cc. and it continued to rise so that after 4 hours the average concentration reached a peak of 13.4 mg. per 100 cc. of free drug. Thereafter the level began to fall and at the end of 24 hours it averaged 5.9 mg. per 100 cc. of free drug. Acetylation of the drug varied somewhat, but reasonable values were obtained. During the first 6 hours an average of 8.7% of the total drug was in the acetylated form. However, in the 12- to 24-hour period the average amount of acetylated drug increased to 15%. At the end of 48 hours no acetylation was evident in 5 of the 8 subjects.

* We are indebted to Dr. W. A. Feizer, Medical Director, Sharp & Dohme, Medical Research Division, Glenolden, Pa., for the sulfamerizine used in this study.

TABLE 1.—FATE OF SULFAMERIZINE ADMINISTERED BY VARIOUS ROUTES
Absorption and Excretion of Single Oral Dose (3 Gm.) of Sulfamerizine

		Amount of sulfamerizine								
		Serum			Urine					
No.	Patient Age (yrs.) Wt. (lbs.)	Time (hrs.)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetyl- ated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetyl- ated (%)	Cumu- lative ex- cretion (%)	Urine vol. (cc.)
1	W. H.	2	12.6	13.7	8.0					
	19	4	12.4	13.1	5.6					
	160	6	10.9	12.5	11.4					
		12	8.6	9.3	7.5					
		24	7.2	8.0	10.0	32.0	47.0	31.9	38.3	2450
		48	3.5	3.2	..	17.4	30.8	43.5	60.3	2150
2	H. K.	2	13.4	15.3	12.4					
	34	4	15.2	17.6	13.7					
	132	6	13.6	16.2	16.0					
		12	9.2	11.2	17.9					
		24	4.9	5.3	7.5	28.4	62.8	54.8	56.0	2675
		48	1.5	1.4	..	12.0	31.0	61.3	72.0	1550
3	G. N.	2	14.7	15.4	4.5					
	23	4	15.5	16.9	8.3					
	150	6	15.4	16.7	7.8					
		12	8.5	12.6	32.5					
		24	7.2	9.0	20.0	88.0	138.0	36.2	70.3	1530
		48	2.6	2.5	..	23.0	42.0	45.2	87.3	1200
4	H. L.	2	12.1	12.6	3.9					
	24	4	12.8	13.8	7.2					
	135	6	11.3	11.0	..					
		12	8.3	9.1	8.8					
		24	6.5	7.1	8.4	42.5	93.8	54.7	32.0	1040
		48	1.9	2.0	5.0	37.4	100.0	63.6	60.3	850
5	J. D.	2	19.1	20.8	8.1					
	20	4	17.3	19.2	9.5					
	145	6	14.9	16.3	8.6					
		12	9.0	9.9	9.1					
		24	3.6	4.7	23.4	136.0	292.5	53.5	61.4	630
		48	0.6	0.6	..	18.0	36.5	50.6	71.3	810
6	A. K.	2	8.2	8.8	6.2					
	23	4	10.1	11.5	12.2					
	125	6	11.9	13.5	11.9					
		12	10.5	12.2	13.7					
		24	5.6	7.5	25.3	27.0	31.3	14.1	25.2	2420
		48	2.7	2.9	6.2	31.6	56.8	44.4	49.4	1280
7	C. C.	2	12.0	13.0	7.7					
	64	4	13.3	14.2	6.3					
	165	6	12.0	13.3	9.8					
		12	9.8	10.9	10.2					
		24	6.3	6.9	8.7	31.0	38.1	18.7	16.1	1265
		48	2.3	2.3	..	24.2	42.4	42.9	35.4	1370
8	D. S.	2	10.5	11.4	7.9					
	17	4	10.7	11.8	9.3					
	147	6	10.4	11.4	8.8					
		12	7.8	8.5	8.2					
		24	6.1	6.9	11.6	50.5	77.5	34.8	21.6	850
		48	2.7	2.8	3.5	32.0	66.4	51.8	31.7	440

Absorption of Single Rectal Dose (3 Gm.) of Sulfamerizine

9	M. R.	2	tr.	tr.
	40	4	tr.	tr.
	135	6	tr.	tr.
		12	1.0	1.0
		24	tr.	tr.
10	A. E.	2	tr.	tr.
	25	4	tr.	tr.
	124	6	tr.	tr.
		12	tr.	tr.
		24	tr.	tr.

*Absorption and Excretion After Parenteral Administration of Sulfamerizine—Intravenous
Injection of Single 3 Gm. Dose of Sulfamerizine Sodium (5%) Solution*

11	E. C.	1	19.3	20.5	5.9					
	17	2	14.3	15.2	5.9					
	122	4	13.4	14.9	10.1					
		6	12.1	12.9	6.0					
		12	10.3	11.6	11.2					
		24	5.7	6.0	5.0	30.2	60.4	50.0	26.0	1290
		48	1.9	1.9	..	12.0	72.2	83.4	47.6	900
12	T. F.	1	20.0	21.2	5.7					
	24	2	17.7	18.5	4.3					
	122	4	14.4	16.2	11.1					
		6	12.0	13.9	13.7					
		12	9.2	10.5	12.4					
		24	4.0	3.9	..	58.0	164.0	64.7	69.7	1265
		48	0.8	0.5	..	5.4	29.6	81.8	80.0	1050

TABLE 1.—(Continued.)

Amount of sulfamerizine										
		Serum				Urine				
Patient	Age (yrs.)	Time	Free	Total	Acetyl-	Free	Total	Acetyl-	Cumu-	Urine
No.	Wt. (lbs.)	(hrs.)	(mg. per 100 cc.)	(mg. per 100 cc.)	ated (%)	(mg. per 100 cc.)	(mg. per 100 cc.)	ated (%)	lative excretion (%)	vol. (cc.)
<i>Subcutaneous Infusion of Single 3 Gm. Dose of Sulfamerizine Sodium (0.5% Solution)</i>										
13	N. G.	2	9.8	10.7	8.4					
	35	6	13.7	15.3	10.4					
	145	12	11.3	12.9	12.4					
		24	7.5	9.2	18.6					
14	F. E.	2	12.5	13.6	8.1					
	51	6	13.3	15.5	14.2					
	145	12	11.1	13.6	19.0					
		24	8.3	10.5	20.9					
15	L. N.	2	11.5	13.0	11.5					
	37	6	12.5	11.8						
	140	12	8.5	10.2	16.6					
		24	4.0	4.6	13.0					
16	J. D.	2	15.0	16.5	9.1					
	33	6	14.0	15.7	10.9					
	133	12	10.8	12.7	14.9					
		24	4.8	6.0	20.0					

Urinary excretion of the drug was measured. Within 24 hours an average of 40.1% of the ingested drug was found in the urine, while after 48 hours only 58.5% had been excreted through the urinary tract. The figures varied from 31.7% in 48 hours to 87.3% in the same length of time. One patient (No. 7), 65 years of age, excreted only 16.1% in 24 hours and 35.4% in 48 hours. During the first 24 hours an average of 37.3% of the excreted drug was in the acetylated form. After 48 hours, however, 50% was acetylated drug.

II. *Fate of a Single Rectal Dose* (Table 1). Two females (Nos. 9 and 10) were given 3 gm. of sulfamerizine in aqueous suspension by retention enema and absorption was studied. At no time was more than a trace of the drug found in the blood.

III. *Fate of a Single Intravenous Dose* (Table 1). Two young males (Nos. 11 and 12) were each given 3 gm. of sulfamerizine sodium in 5% solution in sterile distilled water intravenously. Within $\frac{1}{2}$ hour the average level of free drug was 19.6 mg. per 100 cc.; in 2 hours the concentration averaged 16 mg.; at the end of 4 hours, 13.9 mg.; at the end of 24 hours 4.8 mg. per 100 cc.

IV. *Fate of a Single Subcutaneous Dose* (Table 1). Four males (Nos. 13, 14, 15, and 16) were each given 3 gm. of sulfamerizine sodium, 0.5% concentration in 0.85% saline solution, subcutaneously. Blood specimens were taken at appropriate intervals following administration. In 2 hours the average concentration of free drug was 12.2 mg. per 100 cc., reaching a peak in 6 hours of 13.4 mg., and falling off to 6.2 mg. in 24 hours. Acetylation very closely paralleled that found with the oral administration; about 7% of the total drug in the first 6 hours was acetylated, while in the 12- and 24-hour periods the average acetylation was approximately 16.5%.

V. *Multiple Dosage* (Table 2). Fifteen patients (Nos. 17 to 31, inclusive), suffering from several diseases, including pneumococcal pneumonia, meningococcal meningitis, subacute bacterial endocarditis, and hemolytic streptococcal cellulitis, were treated with sulfamerizine for varying periods of time and with different dosage schedules. Most

of these received an initial dose of from 2 to 3 gm. These patients were divided roughly into four groups: (1) given 1 gm. of sulfamerizine every 6th hour; (2) received 1 gm. every 8th hour; (3) received 1 gm. every 12th hour; (4) 2 patients who received massive intravenous dosages. Variance of the serum concentration of the drug from person to person in the same dosage group was observed and in several instances the degree was marked. In some of these this was obviously the result of change of dosage on clinical indication. In others we have thought it to be due in part to differences in body weight and fluid balance. However, in the same individual the levels were constant. It should be stated, also, that due to the various dosage schedules and hospital routine, the time interval separating the last dose and withdrawal of the blood specimen could not be kept constant in all instances, as these patients were under active treatment for acute infections.

The patients (Nos. 17, 18, 19, 20, and 27) who received 1 gm. of sulfamerizine every 6 hours maintained an average serum concentration of free drug of 13.8 mg. per 100 cc. Levels ranged from 4.7 to 20.5 mg. per 100 cc. In this group the concentration of acetylsulfamerizine averaged 11% of the total drug. The group (Nos. 21, 22, 23, 24, 25, and 26) receiving 1 gm. of the drug at 8-hour intervals showed an average serum concentration of 11.3 mg. per 100 cc. of free drug (range, 3.9 to 19.6 mg.). About 18% of the total drug was in the acetylated form. Two patients (Nos. 28 and 29) received 1 gm. of sulfamerizine every 12 hours. The average level of free drug in the serum was 10.5 mg. per 100 cc. (range, 8.9 to 13.3 mg.). Acetylation in this group averaged 10.2% of the total drug.

Two patients (Nos. 30 and 31) suffering from subacute bacterial endocarditis received large intravenous doses of sulfamerizine sodium. One, a young white male, weighing 154 pounds (70 kg.) received 14 gm. of sulfamerizine by mouth in the first 3 days to check sensitivity. On the 4th day he was given 25 gm. of sulfamerizine sodium intravenously as a 5% solution in sterile distilled water. This solution was given over a 2-hour period. One hour after the infusion had been completed the serum concentration of free sulfamerizine was 106 mg. per 100 cc. Eleven hours later the level had fallen to 79.4 mg. per 100 cc. After 6 days the level was 2 mg. per 100 cc. Nausea was troublesome for several days and it is of interest to note that vomitus obtained 3 days after the last oral dose of the drug and 2 days after the massive intravenous dose contained sulfamerizine in relatively high concentration. The second patient, a young white female who weighed 90 pounds (40 kg.) was managed in the same fashion with the exception that she received 15 gm. of sulfamerizine sodium intravenously. One hour after the end of the infusion her serum concentration of free drug was 90.4 mg. per 100 cc. In 12 hours this had fallen to 73.2 mg. per 100 cc.

A study of the daily urinary excretion of 2 patients receiving 4 gm. of the drug per day showed concentrations of free sulfamerizine ranging from 8.4 to 162.5 mg. per 100 cc. and total sulfamerizine from 18.4 to

TABLE 2.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAMERIZINE

No.	Patient Age (yrs.)	Day	Sulfamerizine						
			Dose (gm.)	Serum			Urine		
				Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetyl- ated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Daily excretion (gm.)
17	H. A. 33	1	4	8.4	18.4	54.3
		2	4	15.5	16.8	7.7	38.6	45.0	16.4
		3	4	20.4	21.8	6.4	162.5	191.3	15.0
		4	4	19.4	20.3	4.4	114.5	153.8	25.5
		5	4	17.9	19.3	7.2			
		6	4	18.4	19.9	8.2			
		7	4	16.1	17.4	7.5			
		8	3	16.5	18.3	9.8			
		9	3	16.4	17.8	7.8			
18	N. D. 28	1	4						
		2	4	5.9	6.7	11.9			
		3	4	8.9	9.8	9.2	32.0	92.4	64.9
		4	4	12.0	13.6	11.8	56.0	151.2	62.9
		5	4	10.9	13.1	16.7	44.2	127.5	65.3
		6	4	9.7	11.7	17.0	54.6	147.5	62.9
		7	4	4.7	5.2	9.6	44.6	140.0	68.1
		8	4	9.8	12.5	21.6	..	41.5	..
		9	0	3.5	3.9	10.3	40.0	145.0	72.4
19	H. M. 17	1	2						
		2	4						
		3	4	13.1	14.4	9.0			
		4	4	16.4	17.3	5.2			
		5	4	15.0	19.8	24.2			
		6	4	15.0	16.8	10.7			
		7	4	16.5					
		8	4	13.5					
		9	3						
20	J. B. 38	10	3						
		11	3	10.1					
		1	5						
		2	4						
		3	4						
		4	4	12.4	13.6	8.9			
		5	4	14.5	16.5	12.0			
		6	4						
		7	4						
21	S. B. 40	8	4	19.5	22.4	12.8			
		9	4						
		10	0	17.0	19.7	13.6			
		1	4						
		2	4						
		3	3	18.2	20.5	11.2			
		4	3	14.0	15.9	11.9			
		5	3	13.8	15.7	12.0			
		6	3	12.7	14.9	14.8			
22	A. G. 30	7	3	13.3	14.5	8.3			
		8	3						
		9	3						
		10	3	14.8	16.7	11.3			
		11	3						
		12	3						
		13	3	16.4	18.1	9.3			
		1	6						
		2	3						
23	W. P. 59	3	3	22.3	24.4	8.9			
		4	3	20.0	22.2	10.0			
		5	3	18.5	20.3	8.8			
		6	3	17.8	19.1	6.7			
		7	3	16.5	17.7	6.7			
		8	3	16.8	18.3	9.1			
		1	3						
		2	3	3.9	5.0	22.0			
		3	3	5.2	7.7	32.5			
24	S. T. 65	4	3						
		5	3	4.4	6.5	32.3			
		6	3						
		7	3	4.5	7.4	39.1			
		8	3						
		9	3	4.4	8.6	48.8			
		1	2						
		2	4						
		3	4	20.8	23.3	10.7			
		4	3	20.3	23.8	10.5			
		5	3	16.2	19.7	17.7			
		6	3	16.9	19.8	14.6			
		7	3	17.4	19.6	11.2			
		8	3	19.6	21.3	7.9			
		9	3						
		10	0	9.6	10.8	11.1			
		11	0	5.1	5.8	12.0			

TABLE 2.—(Continued.)

No.	Patient age (yrs.)	Day	Sulfamerizine						
			Dose (gm.)	Serum			Urine		
				Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetyl- ated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Daily excretion (gm.)
25	M. G. 45	1	3						
		2	3	8.9	12.4	28.2			
		3	3	9.6	13.4	28.3			
		4	3	6.8	9.8	30.6			
		5	3						
		6	3						
		7	3	8.8	11.5	23.4			
		8	3						
		9	3	11.4	16.1	29.9			
		10	3						
		11	3	9.5	12.4	23.4			
		12	3						
		13	3	11.5	16.2	29.8			
		14	3	11.0	13.5	18.5			
		15	3						
		16	3	10.5					
		17	1						
		18	0	6.0					
26	B. O. 68	1	3						
		2	4	19.1	22.0	13.1			
		3	3	25.9	28.9	10.3			
		4	3						
		5	3	12.7	14.8	14.1			
		6	3	14.4	16.5	12.7			
		7	3	14.8	16.0	7.5			
		8	3	18.1	19.4	6.7			
27	H. F. 35	1	3						
		2	4	10.7	15.0	28.6			
		3	4	10.3	15.4	33.0			
		4	0	10.4	14.2	26.8			
		5	0	2.5	2.5				
28	M. R. 40	1	2						
		2	2	8.7	10.1	13.8			
		3	2						
		4	2	11.0	12.6	12.7			
		5	2						
29	M. G. 51	6	2	9.0					
		1	2						
		2	2						
		3	2	13.3	14.5	8.2			
		4	2	12.0	13.0	7.7			
		5	2	10.4	11.4	8.7			
		6	2						
		7	2	9.8	10.9	10.1			
30	R. S. 28	8	2	8.9					
		1	2						
		2	6						
		3	6	22.8	24.6	7.3			
		4	25 (i.v.)	28.5	30.0	5.0			
				106.0*	113.4	6.5			
		5	0	79.4	85.2	6.7	439.0	606.3	27.5
		6	0	44.9	49.2	8.8	459.0	770.0	40.3
		7	0	19.7	21.3	7.4	357.5	516.3	30.7
		8	0	10.0	11.0	9.9	131.0	207.5	36.9
		9	0	4.4	4.4	..	26.3	49.4	26.5
		10	6	2.0	2.0	..	13.1	23.5	44.2
		11	8						0.55
		12	5						
		13	0	26.1					
		1	2						
		2	6						
31	M. G. 17	3	6	21.1	21.9	10.5			
		4	6						
		5	15 (i.v.)	40.7	44.6	8.8			
				90.4*	97.2	7.0			
		6	0	73.2	78.1	6.3			
		7	0	38.5					
		8	0						
		9	6	8.0					
		10	6	24.0					
		11	6						
		12	6	25.6					
		13	6	35.0					
		14	6	35.0					
		15	6	39.0					
		16	6	25.5					

* One hour after intravenous infusion.

191.3 mg. per 100 cc. An average of 50.7% of the excreted drug was in the acetylated form with figures varying from 16.4% to 72.4%. Daily excretion of the drug varied from 26% to 82% of the ingested dose. One patient (No. 45) who received 25 gm. of sulfamerizine sodium intravenously excreted the amazingly high total of 13.09 gm. of the drug in the 2d 24-hour period after the infusion.

B. DISTRIBUTION OF SULFAMERIZINE IN VARIOUS BODY FLUIDS. I. *Cerebrospinal Fluid*. Twelve patients (Table 3) were divided into two groups in order to study the concentration of the drug in cerebrospinal fluid. The first group of 7 patients (Nos. 32 to 38, inclusive) were individuals without meningeal infection, to whom a single dose of the drug was given. Cerebrospinal fluid and blood specimens were then obtained at varying time intervals. Three hours after the oral administration of 3 gm. of sulfamerizine, the ratio of the cerebrospinal fluid level of free drug to that in serum was 0.09. After 6 hours the figure had risen to 0.1, and after 12 hours the cerebrospinal fluid concentration was 0.17 of that in serum. In 24 hours and after two 3 gm. doses the ratio was only slightly higher. The second group of cases included 5 persons (Nos. 19, 25, 39, 40, and 41) with meningeal infection under active treatment. Here the results were quite varied and the ratios ranged from 0.14 to 0.66.

TABLE 3.—FREE SULFAMERIZINE CONCENTRATION IN VARIOUS BODY FLUIDS

Body fluid	No.	Patient	Hours after initial dose	No. of doses	Total dose (gm.)	Serum (mg. per 100 cc.)	Body fluid (mg. per 100 cc.)	Concentration ratio (body fluid/serum)
Cerebrospinal fluid	32	F. M.	3	1	3	11.6	1.0	0.09
	33	P. L.	6	1	3	14.8	1.5	0.10
	34	V. A.	12	1	3	18.4	3.2	0.18
	35	H. A.	12	1	3	15.6	3.6	0.23
	36	P. L.	12	1	3	11.5	1.3	0.11
	37	F. Y.	12	1	3	14.9	3.2	0.22
	38	E. B.	24	2	6	22.5	4.4	0.20
			18	2	6	10.5	5.5	0.51
				(i.v.)				
	39	A. W.	36	4	17	10.0	3.3	0.33
				(i.v.)				
				4				
				(p.o.)				
	19	H. M.	48	8	9	16.1	3.7	0.23
Pleural fluid	25	M. G.	264	16	19	8.8	1.2	0.14
	40	N. D.	30	7	8	8.9	1.6	0.17
	41	L. G.	15	2	3	16.9	11.2	0.66
				(i.v.)				
Pleural fluid	22	A. G.	480	35	37	10.6	10.5	0.99
	42	A. J.	12	1	3	5.9	2.4	0.41
	43	B. P.	12	1	3	8.4	1.7	0.20
Ascitic fluid	44	C. S.	12	1	3	4.4	2.3	0.52
	45	F. G.	12	1	3	6.4	3.6	0.56
	46	B. S.	12	1	3	7.0	3.0	0.43

II. *Pleural and Ascitic Fluid* (Table 3). Sulfamerizine seems to penetrate the pleural and peritoneal cavities readily. In 5 patients (Nos. 42, 43, 44, and 45) who received a single oral 3 gm. dose with simultaneous serum and body fluid specimens taken 12 hours later, from 0.2 to 0.56 of the serum concentration of sulfamerizine was found in pleural and ascitic fluid. In 1 patient (No. 22) after 37 gm. of the drug the serum and pleural fluid concentrations were almost equal.

III. *Erythrocytes and Blood Serum* (Table 4). Simultaneous determinations of sulfamerizine concentration in serum and whole blood were done at different times on 3 patients under continuous dosage. These results indicate a wide variation in red cell and serum concentration and are consistent with the work of others on sulfadiazine.⁴

TABLE 4.—DISTRIBUTION OF SULFAMERIZINE BETWEEN SERUM AND RED BLOOD CELLS

Sulfamerizine Concentration in Mg. per 100 Cc.									
No.	Patient	Day of drug	Whole blood		Serum		Cells (calculated)		Packed cell vol. (%)
			Free	Total	Free	Total	Free	Total	
31	M. G.	18	21.1	23.8	29.5	32.6	7.4	9.5	38
		19	18.1	22.2	26.4	29.6	4.5	10.0	
47	J. M.	2	13.2	..	17.0	..	8.4	..	44
		3	10.5	13.8	17.2	19.9	2.0	6.1	
48	J. H.	3	4.9	6.3	6.0	10.9	2.8	?	35

Discussion. Comparison of this work on sulfamerizine with studies by Reinhold *et al.*⁵ on sulfadiazine (making allowances for differences between whole blood and serum concentrations) indicates that sulfa-

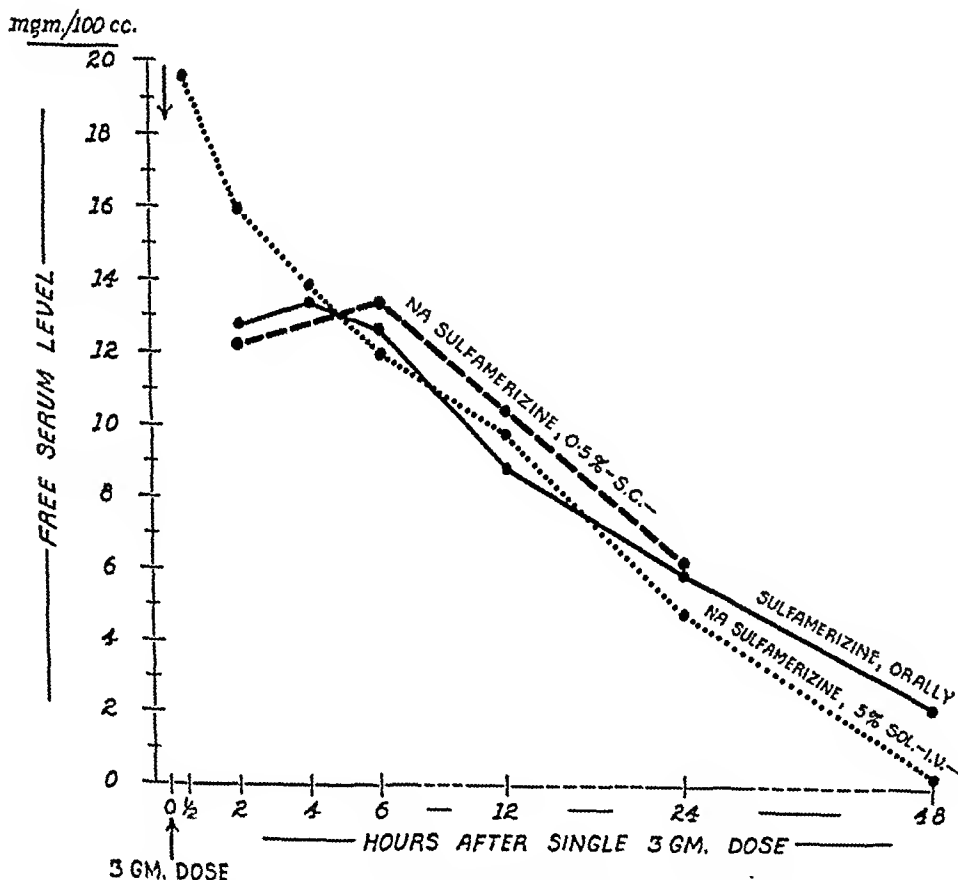


FIG. 1.—Average serum concentration of free sulfamerizine following a single 3 gm. dose by various routes.

merizine is more rapidly and probably more completely absorbed from the gastro-intestinal tract than sulfadiazine. Furthermore, experience with continued administration has shown that smaller doses are

required to attain and maintain a given blood level with sulfamerizine than with sulfadiazine.

Subcutaneous infusion of sulfamerizine sodium results in serum levels closely approximating those obtained when the same dose of sulfamerizine is administered by mouth (Fig. 1). Intravenous administration of sulfamerizine sodium gave high serum concentrations of the drug shortly after injection. However, the serum concentrations and rate of disappearance of sulfamerizine are about the same after the first 4 hours following a given dose, regardless of the route of administration of the drug, except for the fact that sulfamerizine is not absorbed rectally (Fig. 1).

Sulfamerizine penetrates readily into the body fluids studied. However, in view of the experience with sulfathiazole this should probably not be given any great weight in predicting the therapeutic effectiveness of the drug.

The rate of urinary excretion of both free and acetylsulfamerizine relative to dose is about the same as that found with sulfadiazine.⁶ In view of the greater urinary solubility of both the free and acetylated forms of sulfamerizine,⁸ the incidence of urinary complications may be less than with sulfadiazine.

Summary. 1. The behavior of sulfamerizine has been investigated in 28 convalescent patients serving as controls and in 20 patients suffering from acute bacterial infections.

2. The data presented indicate that after a single 3 gm. oral dose of sulfamerizine higher blood serum levels are attained more rapidly and sustained longer than after similar amounts of sulfadiazine.

3. Desired serum concentrations can be obtained by giving sulfamerizine sodium subcutaneously or intravenously.

4. Sulfamerizine is readily distributed through body fluids and enters the red cell in varying concentrations.

5. Sulfamerizine is slowly excreted in the urine in amounts roughly comparable to sulfadiazine.

Dr. J. Harold Austin, Director of the William Pepper Laboratory, showed constant interest and made helpful suggestions during the course of this study.

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CLOT RETRACTION TIME IN THROMBOPHLEBITIS AND PULMONARY EMBOLISM

By J. S. HIRSCHBOECK, M.D.

AND

W. L. COFFEY, JR., M.D.

MILWAUKEE, WIS.

(From the Department of Medicine, Marquette University Medical School, and the Medical Clinics, Milwaukee County Hospital)

THE properties of blood in thrombophlebitis, phlebothrombosis and pulmonary embolism have been studied by several investigators, notably Lampert,⁵ during the last two decades. Valuable contributions to our knowledge of the etiology of these conditions have been made. It is quite generally accepted that the blood platelets and plasma fibrinogen are elevated in most of these cases, particularly when pulmonary embolism has occurred. Barker, Nygaard, Walters and Priestley¹ have demonstrated statistically that anemia is a definite predisposing factor in pulmonary embolism. These 3 hemic factors, blood platelets, plasma fibrinogen and anemia, working together result in a rapid clot retraction time.

The clot retraction time has been observed routinely by hematologists in the study of hemorrhagic diseases. In thrombocytopenia, clot retraction is absent or greatly prolonged. The platelets are considered to be essential for the development of clot retraction because of this phenomena. Hemorrhage may occur with thrombocytopenia even though the coagulation time is normal. On the other hand, thrombosis is also usually associated with a normal coagulation time. This apparent disparity between blood coagulation in a glass tube and within the body has been a problem of great physiologic importance. If a prolonged clot retraction time rather than a prolonged coagulation time is an index of hemorrhagic tendency in thrombocytopenia, it is possible that states characterized by hypercoaguability *in vivo* with normal coagulation times *in vitro* may be associated with a very short clot retraction time.

There may be considerable variation in the clot retraction time in the non-hemorrhagic diseases. Katrakis⁴ demonstrated that in a variety of surgical conditions, more serum was formed during the early 15-minute periods after coagulation in those cases exhibiting cachexia or infection. Lampert⁵ suggested that these observations may explain why some surgical patients have pulmonary embolism. The early formation of serum is the result of rapid and strong clot retraction, and if a thrombus has recently formed in such a patient, it is possible that pulmonary embolism is likely to occur because of the great ease with which the thrombus detaches itself from the vessel wall.

Figure 1 demonstrates that short clot retraction times do occur in association with pulmonary embolism. The clot retraction time was determined by the method of Hirschboeck and Coffey.³ In 9 out of 10 cases of pulmonary embolism, the clot retraction time was less than

10 minutes. In the 10th case, the embolism occurred in a decompensated cardiac patient convalescing from a pelvic operation. The normal clot retraction time varied between 25 and 35 minutes.

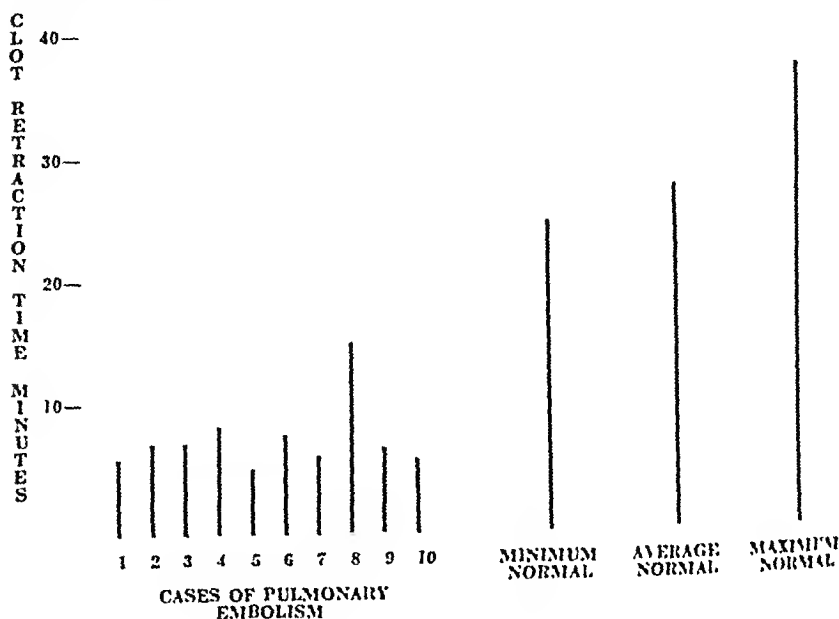


FIG. 1.—Clot retraction time in pulmonary embolism.

The phenomenon of clot retraction has been likened to syneresis. Most gels of all types will, after standing for a period of several days, retract slightly from the walls of their containers. The degree of retraction is slight and does not equal that produced by a blood coagulum. The structure of the true gels and a blood coagulum are entirely different. The blood coagulum is a tangled meshwork of adherent strands of fibrin, whereas a true gel has microscopically an amorphous structure. Although coagulated blood may appear grossly similar to a gel, it is microscopically quite different. Attempts to explain clot retraction in terms of syneresis are therefore not entirely valid.

Inasmuch as the blood platelets are involved in the phenomenon of clot retraction, variations in their number can be expected to influence the clot retraction time. One would anticipate a short clot retraction time with thrombocytosis and a prolonged clot retraction time with thrombocytopenia. This is evidently the case when the number of blood platelets is well above or below the average levels. In a case of chronic myelogenous leukemia with a platelet count of 1,400,000, the clot retraction time was 2½ minutes, while in thrombocytopenia, with platelet counts of 15,000, there may be no clot retraction. These great extremes in platelet counts occur only in the so-called blood dyscrasias and are never encountered in the ordinary case of pulmonary embolism. Although definite elevations in platelets occur postoperatively and during acute infections, they are to an extent capable of only slight

affecting the clot retraction time. Anemia and a high fibrin content are more important in the speed and degree of clot retraction in these conditions.

The sedimentation rate of erythrocytes is, for the most part, determined by the fibrinogen levels of the blood plasma.² When the fibrinogen increases, the sedimentation rate is more rapid. Therefore, blood with a rapid sedimentation rate contains more fibrin when in the coagulated state. It is this increase in the fibrin matrix of the clot which is probably responsible for its more rapid and more forceful retraction.

TABLE 1.—SEDIMENTATION RATE AND ERYTHROCYTE CONCENTRATION IN 126 CLOT RETRACTION TIME DETERMINATIONS

Clot retraction	R.B.C. in hematocrit (%)	Uncorrected sed. rate	Corrected sed. rate	No. of cases
6-10 min.	39.9	40.4	28.4	16
11-15 "	37.4	35.4	24.5	30
16-20 "	45.1	27.6	24.1	25
21-25 "	44.4	22.7	19.9	21
26 min. and beyond	49.0	15.4	16.8	34

Anemia is generally regarded as a contributing factor in the development of pulmonary embolism. With anemia, the erythrocyte concentration, as measured by the hematocrit, is below the normal of 45%. Erythrocytes play an entirely passive rôle in the process of coagulation. After the clot is formed, they, together with the serum, fill up the spaces between the tangled network of fibrin. When retraction takes place, the fibrin strands come in closer relationship to each other and shrink down on the entrapped erythrocytes, and at the same time force the serum out of the clot. In anemia the plasma portion of the blood with its dissolved fibrinogen is proportionally much greater than the erythrocyte percentage. Coagula of anemic blood contains more fibrin, more serum and less erythrocytes than normal blood. When these clots retract, the amount of inert erythrocyte bulk filling the spaces between the mesh is less and the amount of fibrin is more than normal. There is then a more likely probability of rapid and powerful clot retraction. In erythremia the reverse is the case, and here, as might be expected, retraction is very slow or does not take place at all.

This relationship of sedimentation rate and erythrocyte concentration, as measured by the Wintrobe and Landsberg⁶ technique to clot retraction time, is demonstrated in Figure 1.

Heparin as well as other anticoagulants (sodium citrate, sodium fluoride), when used in amounts not large enough to inhibit completely coagulation but merely to delay it, will prolong the clot retraction time. The effect is also produced with heparin when it is given intravenously. Small doses of 100 mg. given at daily intervals will prolong the clot retraction time into the normal range. The mechanism of action of these anticoagulants on clot retraction is not known, but it apparently lies in their stabilizing effect on the blood platelets, reducing their physiologic activity with a resultant thrombocytopenic-like effect on the blood.

Summary. Hemodynamic factors, local tissue and vascular trauma are of great importance as etiologic factors in the development of phlebothrombosis and pulmonary embolism; but anemia and elevation of blood fibrinogen and platelet levels are also of major importance and these working together result in a rapid and powerful clot retraction. The strength and rapidity of clot retraction is perhaps responsible for the loosening of thrombi from vessel walls and explains the coincidence of short clot retraction times with the occurrence of pulmonary embolism. Small amounts of heparin greatly prolong the clot retraction time; the prophylactic use of heparin in patients with short clot retraction times should reduce the incidence of pulmonary embolism.

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A CASE OF EXTREME HYPOTENSION FOLLOWING ACUTE ARSENIC POISONING WITH ADEQUATE BLOOD SUPPLY TO THE TISSUES

BY IRVINE H. PAGE, M.D.

R. D. TAYLOR, M.D.

AND

K. G. KOHLSTAEDT, M.D.

INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital)

THE effect of prolonged periods of excessively low arterial pressure on animals and man has been a subject of interest for many years. Recrudescence of investigation on this subject in its relation-ship to shock has made it seem desirable to publish observations made on a patient recently studied in the Lilly Clinic.

This patient was unusual in that the arterial pressure was very low for a period of about 18 hours, yet he seemed to suffer no ill effects from it, we believe, because the peripheral tissues received adequate amounts of perfused blood, despite the low head of pressure. In this respect the clinical picture differs fundamentally from shock in which the head of pressure is low but peripheral perfusion is inadequate.

Clinical Description. At 9 p.m. a despondent 39-year-old white male took 15 gm. of arsenic trioxide. Within 10 minutes, he began vomiting and retching and had bloody diarrhea. At 11 p.m. he walked into the receiving ward of the Indianapolis City Hospital. His stomach was washed with 2000 cc. of 1:1000 potassium permanganate solution and 1000 cc. of normal saline was started as an intravenous infusion. His arterial blood pressure was 65/35 mm. Hg, pulse rate 94, temperature 98.8° F. One liter of 5% dextrose in distilled water

was added to the infusion at 2 A.M. Mental confusion was noted during the night. At 9.15 A.M. his arterial blood pressure was 45/0 mm. Hg; pulse rate 98. At this time, he felt well and was able to walk and converse. He was a little cloudy mentally, but this confusion was due to a psychosis that later became evident. At 9.30 A.M. he voided in bed. At 10.30 A.M. he was transferred to the Lilly Clinic. He sat up on the cart, walked from the cart to bed with no assistance. His temperature was 97.8, pulse rate 114, respiratory rate 26 per minute and arterial blood pressure was 38 mm. Hg.

The physical findings were hypotension, generalized flushing of skin, absent pupillary light reflex with accommodation reflex present, distant first heart sound and barely audible second sound. Pulse rate was 114. Blood Kline and Kahn reactions were 4+. Red blood cell count was 5.27 million; white blood cell count 21,400; hemoglobin 90.3%; hematocrit 36.0%. Total plasma proteins were 7.2 gm./100 cc. Blood urea nitrogen 37.6 mg. per 100 cc.; blood chloride 584 mg. per 100 cc.; blood calcium 9.1 mg. per 100 cc.; blood phosphorus 4.9 mg. per 100 cc.; venous blood CO₂ combining power was 30.8 vol. per 100 cc.; arterial CO₂ combining power was 29.3 vol. per 100 cc.

Skin temperatures were 33.75° C. on left arm; 33.0° C. on right arm; 36.0° C. on left abdomen; 35.5° C. on right abdomen; 33.25° C. on left leg, and 33.5° C. on right leg.

The ECG was interpreted as being normal and ballistocardiographic tracings were normal with pulse rate of 112; stroke volume per 1.73 sq. meters body surface was 82 cc. (normal 70 cc.); and cardiac output 5.3 liters per 1.73 sq. meters/minute (normal 2.8 liters). Peripheral resistance ($R = 3 \text{ Pm/CO}$) was 17 (normal 100).

Peripheral pressor substance as measured by perfusing plasma through an isolated rabbit's ear and ascertaining the amount of vasoconstriction¹ was comparable to normotensive person's during the period when the patient's arterial blood pressure was 48 mm. Hg mean pressure and later 60 (76/44 mm. Hg). Renin-activator as measured by the activation of human renin in a pithed cat was present in amounts comparable to a normotensive.

With so many normal findings in a patient apparently little disabled by the poison, the accuracy of the auscultatory measurement of arterial blood pressure was questioned. A 19-gauge needle was inserted into the femoral artery and connected to a mercury manometer. Mean arterial blood pressure was 30 mm. Hg. Intravenous angiotonin (4.5 cc.) given over 5 minutes time gave a rise in mean pressure to 98 mm. Hg with no change in pulse rate. Intravenous injection of 3 cc. of 1:10,000 adrenalin given over a 2-minute period gave a rise in mean pressure to 136 mm. Hg and tachycardia of 140. At the completion of these studies, it was 12.30 P.M., or 15½ hours since ingestion of arsenic. The patient had become anuric. As noted above, he voided in bed at 9.30 A.M. There is no way of knowing how long this urine had been in his bladder.

During the morning he was coöperative but talked with slurred speech of grandiose matters. He ate an egg sandwich and drank 2 glasses of milk. Immediately following this, he had a chill lasting 20 minutes. His temperature rose to 103° F. His arterial pressure varied from levels which were imperceptible by the auscultatory method to 40 mm. Hg systolic, levels too low to filter urine through the glomeruli of the kidneys. Following the chill, he became more irrational and quite violent, necessitating restraint. At 4.45 P.M. an infusion of 1000 cc. of normal saline was started. Three hours later he was quiet and coöperative. He had a bloody stool, the first time since admission. He was still anuric with systolic blood pressure of 40 mm. Hg. At this time an infusion of plasma was started simultaneously with an infusion of 500 cc. of normal saline containing 50 cc. of angiotonin. The blood pressure was maintained at 70 to 100 mm. Hg systolic by regulating the drop rate of angiotonin. On one occasion the inflow of angiotonin was increased to elevate the arterial blood pressure to 130/80 mm. Hg. At this pressure level, he talked in a wild manner, struggled and fought the attendants. By decreasing the infusion rate, blood pressure was reduced to 70/40 mm. Hg. He became calm and quiet but was still grandiose.

At 10.45 p.m., 25 hours after taking arsenic, angiotonin was discontinued. By infusing normal saline rapidly, arterial blood pressure was maintained at 70 to 90 mm. Hg systolic and 30 to 40 mm. Hg diastolic until midnight. At this time, 15 cc. of urine were obtained with a catheter. The specific gravity was 1.022; it was loaded with granular (80%) and hyaline casts (20%); there were 20 to 30 white blood cells and 5 to 10 red blood cells per high-powered field. Curiously, there was no protein present. At 1 a.m. arterial blood pressure had fallen to 64/30 mm. Hg. Ephedrine, gr. 3, was given subcutaneously. This was followed by a rise in pressure to 100/40 mm. Hg. He again became violent, grandiose and abusive. Sodium phenobarbital administered subcutaneously induced sleep for the remainder of the night. At 8 a.m. 40 cc. of urine was obtained by catheter. During the morning of the second day 2000 cc. of 10% glucose in water were given intravenously. Two-and-a-half hours later he voided 600 cc. of urine. Specific gravity was 1.004; it was free of casts, white blood cells and protein. Dr. R. N. Harger found 1 mg. of arsenic per liter of urine. Blood urea nitrogen was 59.5 mg. per 100 cc.

Aside from mental confusion and occasional attacks of violence, he was apparently quite well. Arterial pressure maintained itself between 100 and 120 mm. Hg systolic and 40 to 60 mm. Hg diastolic. Cardiac output was 4.53 liters/1.73 sq. meters/min. (normal 2.8 liters) and stroke volume was 77 cc. (normal 70 cc.). Red blood cell count was 4.35 million; peripheral resistance was 53 (normal 100); white blood cell count 15,500; hemoglobin 86.1%; and hematocrit 36%. Blood urea nitrogen had fallen to 41 mg. per 100 cc. Coreoran of this laboratory measured renal blood flow by diodrast clearance on the 4th day after ingestion of the poison and found it to be 669 cc. per min. Inulin clearance was 33.9 cc. per min.; filtration fraction, 0.08.

With blood pressure at normal levels, and patient voiding, it was possible to investigate more freely the notion that the patient had central nervous system syphilis as well as arsenic poisoning. The pupils showed the Argyll-Robertson phenomenon, speech was slurred, delusions of grandeur were present, and the blood Kline and Kahn reactions were positive.

The patient's mother furnished the history later relative to his mental changes. She stated that his mind had become more and more childish over the past 2 years. He often made claims of wealth and prestige that were utterly false. The cerebrospinal fluid pressure was 220 mm. of water. The fluid gave a 4+ Wassermann reaction; 2+ globulin reaction; gold curve was 555443110; cell count 9 lymphocytes. The diagnosis of general paresis was confirmed. From this time on, his course was that of fulminating paresis with increasing stupor, abdominal distention, hyperpyrexia and death, 10 days after ingestion of the arsenic trioxide.

Postmortem examination of the brain confirmed the diagnosis of general paresis. There were no gross lesions in either the thorax or abdomen. Sections taken from the liver and kidney examined by the Coroner proved to be normal.

Discussion. The observations on this patient suggest that arterial blood pressure may be profoundly reduced and remain so over long periods of time without causing pathologic changes. Despite the fact that the mean arterial pressure, measured by femoral arterial puncture, was only 30 mm. Hg, he was able to walk and coöperate satisfactorily. Indeed, when the blood pressure was raised to normal level by plasma and angiotonin he tended to become dis-oriented. It is of especial interest that at no time was his skin pale or cold as in the state of shock. On the contrary, it was warm and at times flushed. We assume that these signs signified adequate perfusion of the tissues with blood. The hemodynamic changes associated with the low arterial pressure were interesting. Cardiac output was nearly doubled, due to increased

stroke volume and rate, while peripheral resistance was only about one-fifth of normal; in short, conditions making for excellent perfusion of the tissues.

The renal vasopressor system was apparently not called into play by the reduced pressure, as no increase above normal in either the peripheral vasoconstrictor substance or renin-activator was found. Peripheral vasoconstrictor substance (P.V.C.S.) has been found by Page² in the plasma of hypertensive patients and animals and in normotensive animals after injection of renin. Its chemical nature is not known. It is determined by perfusing small samples of the unknown plasma through an isolated rabbit's ear perfused with blood. When plasma containing or forming peripheral vasoconstrictor substance (P.V.C.S.) is injected, immediate constriction occurs in the vessels of the ear.

Renin-activator was determined because several years ago it was shown³ that in hypertensive patients the amount of it is increased. Presumably this increase is a response on the part of the liver to the increased need for this substance, for it has been shown that the liver is the source of renin-activator.⁴

The response to intravenously injected angiotonin was excellent and it was possible to keep the arterial pressure elevated by simultaneous injection of angiotonin and plasma. The maintenance of pressure was evidently largely due to the angiotonin because when it was temporarily discontinued, despite continued administration of plasma, the arterial pressure fell. Since the heart rate did not rise during the angiotonin administration it seems reasonable to suppose that the elevation in pressure was due to increased arteriolar resistance and augmentation of the force of the heart beat.⁵ In fact, after the blood pressure had been restored to nearly normal, the peripheral resistance rose from 17 to 53.

Since the blood pressure was well below the level necessary for glomerular filtration, it is not surprising that there was a period of anuria. This was followed by partial recovery of renal function and blood flow by the 4th day after poisoning.

This clinical experiment suggests to us that arterial pressure may be profoundly reduced without serious damage to tissues other than the kidneys if tissue perfusion is still adequate.

We have searched the literature for similar studies on the effect of arsenic trioxide and other arsenic compounds on arterial pressure. A few suggest that these substances elevate blood pressure and a few that they lower it. None carry conviction.

It is interesting that the patient suffered from general paresis and that many of his mental symptoms were expressions of that disease. Administration of large amounts of inorganic arsenic appear to have reactivated the disease, a not uncommon occurrence seen in ill-advised therapeutic attempts with organic arsenic compounds.

Summary and Conclusions. A parietic was studied who took 15 gm. of arsenic trioxide with suicidal intent. We were amazed to find that he was able to walk and coöperate despite the fact that mean intra-

arterial blood pressure was only 30 mm. Hg. The other striking feature was that tissue perfusion seemed excellent; the only function appearing to suffer being the ability of the kidneys to secrete urine.

The patient was able to maintain adequate perfusion of the tissue by doubling the output of the heart and greatly reducing peripheral resistance. The renal vasopressor system did not respond to the hypotensive stimulus possibly because pulse-pressure was not reduced.

Infusion of angiotonin and plasma restored the arterial pressure to normal after a period of about 18 hours severe reduction.

The patient seemed to have few ill-effects from this episode except that, associated with it, reactivations of general paresis occurred, from which he had previously suffered, leading to his death.

This clinical experiment suggests to us that reduction in arterial pressure need not lead to serious consequences if the perfusion of the tissues remains adequate. In this respect the clinical picture was the reverse of shock in which both arterial pressure and tissue perfusion are severely reduced. The importance of obtaining better tissue perfusion in shock rather than elevating arterial pressure—the converse of the hemodynamic state in our patient—is suggested by these observations.

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PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK CITY

AND

SOMA WEISS, M.D.

HERSEY PROFESSOR OF THE THEORY AND PRACTICE OF PHYSIC AT HARVARD UNIVERSITY
BOSTON, MASS.

ESTROGENS AND ANDROGENS

By S. CHARLES FREED, M.D.

MT. ZION HOSPITAL, SAN FRANCISCO, CAL.

Estrogens. Compounds. Following the clinical availability of pure potent-estrogens there were published numerous enthusiastic reports on the successful treatment of a wide variety of endocrine and non-endocrine conditions. There has been sufficient time now, however, for the resulting confusion to have cleared considerably, and the actual worth of estrogens to be evaluated on a relatively sound basis. In the past few years, estrogen therapy has been firmly established on a scientific rationale and additional experimentation has furthered our knowledge of this subject. Some of the more recent developments are centered on improving the known estrogens for therapeutic purposes, as well as the introduction of entirely new compounds. The two most commonly used natural estrogens, estrone and estradiol, have been modified in several ways so as to render them more efficient. The methods used in modifying these estrogens rest upon the fact that they are rather readily destroyed when introduced into the animal body. It has been conclusively demonstrated that they are destroyed by the liver, either by conjugation with glucuronic acid or through alterations to metabolic by-products and excreted in such forms.

Estradiol can be combined with certain common inert substances so as to lessen the destruction by the body. Thus, the compounds estradiol benzoate and dipropionate are more efficient than the free compound, because of the fact that these compounds have a decreased rate of absorption at the site of injection so that the estrogen enters the blood stream at a slower rate and over a more prolonged period of time. This mechanism resembles that of the ovaries which also elaborate estrogen in relatively small amounts but at a slow rate. Estrone cannot be combined with inert substances with advantage and therefore suffers in this respect. Another compound of estradiol, recently introduced, is ethinyl estradiol which is apparently more potent by mouth than any other compound of

estradiol. This preparation was designed to meet the increasing demand for more convenient estrogen therapy which is made available through oral administration. In this respect, one of the newest available natural estrogens is estrone sulfate. This substance occurs in the urine of pregnant mares together with sulfates of the other naturally occurring estrogens. From laboratory experiments, it is claimed that this compound is 3 times as potent orally as free estrone. In human experiments it has been proven to be potent by mouth in dosages somewhat smaller than one would expect by application of laboratory data.

Probably the most efficient means of supplying estrogens for clinical purposes, where long-continued applications are desired, is with the use of crystals of estrogens or pellets made from crystals, which are introduced by subcutaneous implantations. Since the estrogens are steroids and water-insoluble, these implants dissolve slowly in the tissue fluids at the site of implantation, and therefore are absorbed very slowly into the blood stream. Such implants will produce an estrogenic effect over long periods of time without additional therapy. Bennett and Te Linde⁸ maintained that of all the methods of estrogenic therapy they have used, the one using the implantation of crystalline estrone is the most effective method yet devised for combating the menopausal syndrome, where long-continued effects are desired. These authors did not use any other natural estrogens in pellet form. It has been reported, however, that pellets may fail to be absorbed after some time because of the connective tissue scarring about the pellets. Another disadvantage to pellet implantations is the inconvenience of this type of therapy, although the technique used formerly by incision has been supplanted by the use of large bore needles with a trocar for inserting the pellets. Physicians seem, however, loathe to use pellet implants in general practice. For this purpose, therefore, a method has been devised which utilizes the principle of crystal implantation, but by simple intramuscular injections with an ordinary syringe. Thus, estrone crystals have been suspended in aqueous solution.²⁴ This material is drawn into an ordinary syringe and injected intramuscularly. The aqueous medium is absorbed rapidly leaving a small deposit of crystals. While such a technique does not, of course, parallel the results following the deposit of large pellets or a large amount of crystals it appears to be the most satisfactory method of administering estrone with an ordinary syringe. In addition, the use of an aqueous suspension of crystals does not introduce the possibility of sensitivity reactions to the oil vehicle common to most injectable estrogens.

Great strides have been made with the introduction of synthetic estrogens. Not only has this resulted in the availability of estrogens at economic cost, but has opened up new fields for estrogen therapy because of the ease of administering large dosages of estrogens. These synthetic estrogens may be and most commonly are, administered by mouth. Most attention has been given to the first highly potent synthetic estrogen developed, namely diethylstilbestrol. This estrogen prepared from non-biologic materials is capable of producing most of the physiologic effects of natural estrogens. There is some slight difference in the metabolic and pharmacologic reactions of this material from that of the natural estrogens. There was considerable resistance in this country to the acceptance of this substance because of the early reports regarding its possible toxicity since experimental work had demonstrated that the compound might impair the function of the liver and bone marrow and cause certain unpleasant symptoms following its administration in large

Both the Food and Drug Administration and the Council on Pharmacy and Chemistry have accepted this compound on the basis of clinical and laboratory reports which claim that this compound is no more toxic than natural estrogens in equivalent dosages.⁵⁴ Since its official acceptance, only two reports have appeared which would indicate the possibility of harm arising from its use and these reports concern 2 cases where allergic response to diethylstilbestrol were encountered. The origin of nausea and other disagreeable symptoms which are relatively frequent complications of diethylstilbestrol therapy have been shown rather satisfactorily to be on a physiologic basis of non-specific nature rather than from any pathologic lesion.²² Thus, Freed and associates have maintained that nausea following diethylstilbestrol administration is a result of its rapid absorption into the blood stream giving rise to symptoms which could be explained on the basis of water retention in the tissues. Thus, headache is produced by cerebral edema, nausea from edema of the gut, etc.²⁵ When the absorption of diethylstilbestrol is delayed through combining it with a fatty acid, toxic symptoms are reduced. Greene and Ross have demonstrated that diethylstilbestrol dipropionate gives rise to disagreeable symptoms less than half as frequently as the free compound.³³ In this respect, Freed and associates have shown that diethylstilbestrol dipalmitate gives rise to little or no disagreeable symptoms and has a remarkably prolonged beneficial action in the menopause because of its unusually slow absorption at the site of injection.

Diethylstilbestrol has also been used in the form of pellets, but this does not appear to be satisfactory, inasmuch as oral therapy is more readily controlled and quite convenient.⁴⁷ Considerable experimentation has been made with the monomethyl ether of diethylstilbestrol or methylstilbestrol. There is some controversy as to its advantages over the free compound.^{13,19} Dihydrodiethylstilbestrol or hexestrol has also been used. There is some evidence that this is somewhat less toxic than the parent compound, although it is reported in this country to be from one-fifth to one-tenth as active. An entirely different synthetic estrogen has been recently made available commercially. This compound is called Octofollin (118B) and has no relationship chemically to diethylstilbestrol or the natural estrogens. It has the formula 2, 4-di (para-hydroxyphenyl)-3-ethyl hexane. It has been shown to be a potent estrogen by laboratory and clinical experimentations.^{12,26} Robson and Schönberg have introduced another new estrogen which has a prolonged action when given orally.⁵⁶ It is a derivative of triphenylethylene with the formula, alpha, alpha-di-(para-ethoxyphenyl) beta-phenyl bromo-ethylene. This compound is called for convenience, D.B.E. This substance is the only estrogen known that has a prolonged action when given by mouth. It is thought to be stored in the body and released slowly to produce its prolonged effect. There are as yet no clinical reports on this substance. Still another estrogen of promise, which has been shown to be effective in relatively small doses, is 8-di-p-hydroxy-phenyl- Δ B8 hexadiene or more conveniently "dinestrol." Barnes has shown it to be about 10 times as potent as diethylstilbestrol in the suppression of lactation when administered by mouth.⁶

Therapy. Following the initial deluge of reports on the use of estrogens for a wide variety of conditions, there has developed a far more sound point of view on the indications and contraindications for estrogen therapy. Most authorities, including the Council on Pharmacy and Chemistry, have recognized that estrogens are worthwhile in conditions such as the

menopause and its complications, senile vaginitis, kraurosis, and gonorrheal vaginitis of infancy. With the introduction of higher dosage forms of estrogens following the development of the synthetics, the Council included in its list of indications the suppression of lactation and prevention of painful breast engorgement. A number of other conditions have been subjected to therapeutic trials with estrogens with promising results, although definite conclusions cannot be drawn as to the ultimate value of such therapy. These conditions are functional uterine bleeding, dysmenorrhea and a variety of non-endocrine disorders.

In the treatment of menopausal symptoms, estrogen therapy is on a far more satisfactory basis than before. The synthetic estrogens have offered inexpensive products with a wide flexibility of range for administration. The oral administration of such estrogens relieves the patient of frequent visits to the physician for hypodermic injections. It is considered advisable to administer such estrogens cyclically with frequent rest periods. The commonly used synthetic diethylstilbestrol has an average dose of 0.5 to 1 mg. daily. The chief disadvantage of this compound is the development of unpleasant symptoms in a significant percentage of patients. While no actual tissue damage is produced the untoward symptoms may cause many patients to refuse to undergo such therapy. It is known that the incidence of the disagreeable symptoms, chiefly nausea, dizziness and headache, is in proportion to the size of the dose. Therefore, if therapy is started with small amounts, some patients may be spared the development of these reactions. Enteric coating, bile salts, alkali and various other procedures claimed to eliminate the toxicity are of doubtful value in view of the fact that these symptoms are of systemic, not local, origin.

The use of other compounds of stilbestrol has been tried to a considerable extent. Hexestrol is effective in doses which are considerably greater than those of diethylstilbestrol. This, however, should cause no objection because the cost of the active material is practically insignificant in therapeutic doses. Freed and associates found that 2.5 to 5 mg. daily of hexestrol is the average therapeutic dose.^{25,27} Bieren and Compton² found that 10 mg. daily appears to be a satisfactory dose. The incidence of toxicity is reported to be somewhat less than for diethylstilbestrol. Methylstilbestrol has also proven to be an effective estrogen. There is some disagreement, however, as to the actual potency of this material. Geschickter and Byrnes²⁹ maintain that 2 mg. daily is an effective dose which is also equivalent to that of diethylstilbestrol. Abarbanel¹ maintains that the monomethylether is one-fifth as active as the parent compound.

Oral estrogens other than the stilbenes have been developed which may prove satisfactory. Octofollin is approximately one-half as active as diethylstilbestrol, according to Freed and associates.²⁷ In therapeutic doses there are relatively few toxic reactions. These results have not been confirmed as yet in published articles while Taylor and Thompson³⁰ have failed to confirm these results. As yet this compound has only been used in the treatment of the menopause. Menopausal patients have been encountered where bleeding appeared following octofollin therapy and the author has been able to induce bleeding in a few cases of amenorrhea.

The natural oral estrogens used in the newer treatment of the menopause are ethinyl estradiol and estrone sulfate. While there is considerable evidence that the former is active in doses of 0.5 to 1 mg. daily, there is evidence that at this dosage level the material may be toxic and therefore

possess no advantage over the stilbenes.⁵⁸ Estrone sulfate has been available on the market too recently for a complete evaluation. Nevertheless, the early evidence points to the fact that in the dosage of 1 mg. daily, most patients will obtain satisfactory relief from their symptoms.²⁷ It has also been noted that patients may prefer this estrogen to some of the stilbene compounds because it gives a greater sense of general relief. It has been suggested that while diethylstilbestrol may eliminate some of the symptoms of menopause, such as hot flashes, they fail to give this feeling of well-being. It is possible that it often induces a low grade toxic reaction which is insufficient to be considered definitely a disagreeable symptom such as nausea or headache, but is interpreted by the patient as a failure to feel well.

The use of pellet implants is a most efficient form of therapy, since the administration of 25 to 50 mg. of an estrogen in a pellet will afford relief for a number of months without additional therapy. In fact, Salmon and associates⁵⁸ maintain that the implantation of estrogen crystals before castration will prevent the appearance of symptoms for many months, and as long as 2 years in a number of patients. Bennett and Te Linde⁸ recommend pellet implants of estrone as the most effective method devised for combating the menopausal syndrome. However, pellets are not yet available on the market. There is a possibility that some of the estrogens may be improved further so that even pellets may not be considered to possess advantages. In this regard, Freed and associates have introduced diethylstilbestrol dipalmitate.²⁶ This combination of estrogen with a relative high fatty acid was injected in dosages containing 5 mg. of the active compound 3 times at weekly intervals. The period of relief from symptoms following cessation of therapy averaged 8 to 9 weeks. In some unpublished work the author has found that one injection of a 5 mg. dose in about 200 instances produced relief, on the average, for 5 weeks. It is obvious that compounds developed along these lines with, for instance, even higher fatty acid esters may be even more effective, or that an injection of 10 or 15 mg. will produce results equivalent to that of pellets.

The ability of estrogens to suppress lactation has been established rather satisfactorily following the introduction of the synthetic estrogens. Diethylstilbestrol, chiefly, has been used for this purpose.^{1,15,64} The natural estrogens appear to be equally effective, but have the disadvantage of being costly. Inasmuch as lactating women are tolerant to diethylstilbestrol compounds, there appears to be no drawback to the use of these synthetic compounds in this condition. It has been adequately proven that the administration of these estrogens is more effective in the early postpartum period, and that the estrogens have little effect on lactation where nursing is maintained.¹ Dinestrol has been shown to be 10 times as potent as diethylstilbestrol in suppressing lactation.⁶

Estrogens have been demonstrated to be effective in relieving the pain of patients with dysmenorrhea. The administration of estrogen for this purpose depends, according to some workers, upon suppressing ovulation.⁶⁵ The material is injected or administered orally in the first 2 weeks of menstrual cycle, thereby suppressing the gonadotropic hormones of the anterior pituitary so that the subsequent menstrual period becomes anovulatory preventing the pain which has been claimed to be dependent upon the presence of the corpus luteum. Hirst and associates³⁹ have obtained satisfactory results with this therapy but do not agree that relief is due to suppression of ovulation.

One of the more promising features of estrogen therapy recently developed is the treatment of uterine bleeding. Karnaky⁴¹ demonstrated that estrogens in sufficiently high dosage will stop practically any type of uterine bleeding. The dosages are rather high, as much as 25 mg. of diethylstilbestrol daily. He maintains that the bleeding from fibroids, polyps, tubal pregnancy and functional conditions may be effectively combated in this manner. He has also demonstrated that the injection of estrogens directly into the cervix will bring prompt suppression of bleeding. Confirmation of this work has not been published except for the work reported by Palmer,⁵⁰ and Cuyler and associates,¹⁶ who have demonstrated that diethylstilbestrol is effective in suppressing functional uterine bleeding. It appears that the functional bleeding of meno-metrorrhagia in the premenopausal period may be controlled by relatively small dosages of estrogens. In younger women, the excessive bleeding of menorrhagia apparently requires much larger doses of estrogens. The biphasic nature of the therapy of functional bleeding is based on two factors. In the suppress the anterior pituitary in order to reduce the activity of the ovary. This is brought about with large doses of estrogens. Certain types of bleeding, especially that found in the premenopause, may be due to a diminished ovarian secretion of estrogenic hormone resulting in a lowered blood estrogen level, in the neighborhood of the bleeding threshold of the uterus, so that the minor fluctuations in the blood estrogen level cause intermittent bleeding or spotting. Raising the blood estrogen level above the threshold with relatively small dosages prevents bleeding.

The earliest work on estrogen therapy indicated that patients with involutional melancholia would respond to estrogen therapy. The work of several psychiatrists seems to indicate that only occasionally does this condition respond to estrogen therapy.^{51,52} Apparently the disparity in results depends to a certain extent on the diagnosis of this condition. It is possible that severe menopausal symptoms including depression may be interpreted as melancholia. On the other hand, some investigators considered that true melancholia is an irreversible condition due to degenerative changes in the brain, and that estrogen therapy does not affect the mental status although it may clear up subjective symptoms in the patients.

Reynolds and others⁵³ have shown that there may be certain psychogenic factors in the menopause apart from the vascular instability. Such patients do not respond well to estrogens.

Another psychic disorder which has been treated by estrogens is hypersexuality in males. Dunn⁵⁴ has demonstrated that 5 mg. daily of diethylstilbestrol decreased the libido in a hypersexual male but that the condition returned 9 to 16 weeks following therapy. This work might indicate that hypersexuality is actually due to an overproduction of androgen.

Considerable work has been done on the metabolic effects of estrogens. It has been demonstrated that estrogens will induce retention of sodium and water in the body and that this retention follows usually the retention level of the blood. It was postulated by Greenhill and Fries⁵⁵ that premenstrual tension resulted from such a retention of fluids in the various organs giving rise to symptoms depending upon which organ was involved. They have administered ammonium chloride to combat the retention of fluid and have shown that the symptoms were dramatically relieved. Albright and associates⁵⁶ have studied the relationship of calcium and

olism to ovarian function. They have shown that there is a loss of calcium from the bone after ovarian failure and that many of the fractures of elderly women were due to the resulting porosity of the bone. They demonstrated that estrogen administration produces a more rapid healing of such fractures, due to the increased deposition of calcium in the bone.

Albright and workers⁴ have demonstrated an interesting syndrome characterized by sexual infantilism together with dwarfism. This syndrome has also been described by Varney, Kenyon and Koeh.⁶⁷ Treatment of this condition may be satisfactorily performed by estrogen.

Salmon and coworkers⁵⁸ have described a syndrome characterized by dysuria and incontinence in postmenopausal women due to atrophy of the urethral mucosa and impairment of sphincter function. Estrogen therapy brought relief to most of these patients, which was paralleled by growth changes in the vaginal mucosa.

Considerable interest has been aroused in the possibility of treating cancer of the prostate by endocrine preparations. Associated with this particular kind of malignant neoplasm there is often an increase in the acid phosphatase of the blood, especially if metastases have occurred. The administration of estrogens is followed by a reduction of this acid phosphatase and by an improvement in the clinical condition of the patient in the majority of cases. Huggins and associates,⁴⁰ who demonstrated that estrogens ("chemical castration") were of value in relieving the pain and bladder discomfort, also demonstrated the beneficial effects of castration in this condition. In a symposium at the 1942 A. M. A. Session, Alyea and Henderson^{4a} claimed that castration caused marked improvement in many of these patients, as well as relief of pain from metastases, urinary obstruction and infection. Diethylstilbestrol was of value but not as effective. Creevy,^{15a} however, was not as enthusiastic over these forms of therapy, but recognized them as palliatives in the late cases. Thompson^{66a} considered orchidectomy and diethylstilbestrol as valuable adjuncts to prostatectomy. Nesbit and Cummings^{48a} believed castration a worthwhile procedure in advanced cases when little aid was obtained from diethylstilbestrol therapy. Gutman^{34a} regarded the data on diethylstilbestrol therapy as inconclusive. Apparently, dosage and appraisal of results are variables which must be controlled rigidly for better evaluation of the therapeutic response. The common factor in castration and estrogen therapy is the cancellation of androgen secretion of the testes which may stimulate the growth of prostatic cancer tissue.

Standardization. Several investigators have recently expressed the opinion that the therapeutic efficiency of an estrogen can be judged only by testing its potency in the human. Most claims for the relative therapeutic effectiveness of estrogens have been made on the basis of their activity as determined in laboratory animals, principally the rat or the mouse. The assumption that data so obtained can be accepted for the human has resulted in considerable confusion in the standardization of estrogen therapy. In the first place, results obtained from assays differ widely, as indicated by the fact that the rat unit of estrone as determined in different laboratories varies as much as several thousand per cent when compared to a weighed amount of crystalline material; the same holds true for assays in the mouse. The discrepancy in the assay of estrogens in the rat or the mouse cannot be entirely accounted for by technical differences in the performance of the assays, and it appears quite certain that each strain of rat or mouse has a different degree of sensitivity to any one estrogen. Similarly, comparisons of the potencies of different estrogens

such as estrone and estradiol in the same laboratory cannot be judged as the true reflection of the relative therapeutic potencies of these substances inasmuch as the ratios of activity as determined by different laboratories are far from constant. A recent article, a compilation of data on this subject reported by a number of investigators, illustrates the inconsistencies in animal assays and lead to the conclusion that any statement regarding the relative therapeutic activity of estrogens on the basis of animal assays is subject to considerable error, and assays in the human is at the present time the only hope for satisfactory therapeutic standards of estrogens.²¹

Several attempts have been made to assay the activity of estrogens in humans. Some investigators have utilized changes in the vaginal mucosa of menopausal patients following estrogen administration as an index of estrogen activity, much the same way as the castrate rodent is used. When it is recognized, however, that untreated menopausal patients have varying degrees of proliferation of the vaginal mucosa, it does not appear that this would be a satisfactory means of assay. There is a lack of evidence that the vaginal epithelium of a group of menopausal women will respond to a definite amount of estrogen with a sufficient degree of uniformity. Furthermore, the reading of vaginal smears in the human for assay purposes is liable to considerable experimental error. Several authors have expressed their dissatisfaction with the use of vaginal smears for assay purposes.^{7,22} An attempt has been made to utilize the changes in the menopausal endometrium following estrogen administration as a means of assay.⁶⁹ Such a technique is not only cumbersome but is also open to more criticism than that mentioned above for the use of vaginal smears, inasmuch as untreated menopausal patients may possess sufficient degrees of endometrial proliferation and, in fact, hyperplasia.⁴⁹ This factor would interfere greatly with assays based on endometrial changes.

Bennett⁷ has failed to find reliable data in human assays of estrogens based on four objective tests: 1, vaginal smears; 2, depression of gonadotropin excretion; 3, estrogen excretion; 4, changes in the cervical glands. He believes the subjective relief of menopausal patients the most reliable criteria. Mack and Ale⁴⁷ used the glycogen content of vaginal smears for assaying estrogens.

The author has selected the subjective response of menopausal patients as an end-point in the human assay of estrogens. It was acknowledged that the evaluation of such a response may be obscured by numerous uncontrolled factors. Nevertheless, this method has been selected for the assay for a number of reasons, not the least of which is the fact that the chief purpose in administering estrogens is to relieve the menopausal patient of her subjective symptoms. Such an assay requires no special technique and a large number of patients may be included in a study with little difficulty. In order to eliminate as many distracting factors from this study as possible, certain rules were established. Patients who complained of symptoms which were due to psychic changes due to environmental or social complications were not included in the group tested. The patients treated, complained of at least two to four hot flashes daily together with other symptoms commonly found in the premenopause such as nervousness, irritability and emotional instability. The psychic factors associated with any form of therapy involving subjective sensations were reduced to a minimum by eliminating any therapeutic suggestion such as a promise of beneficial results or leading questions concerning the therapeutic responses. In addition the subjective changes

of all the patients were evaluated in as constant a manner as possible. Furthermore, the estrogens were administered in several dose levels in the manner which is used for assaying estrogens in laboratory animals. Three synthetic estrogens, hexestrol, diethylstilbestrol and octofollin, were thus assayed. A satisfactory therapeutic dose of diethylstilbestrol is 0.5 to 1 mg. daily, hexestrol 2.5 to 5 mg. daily and octofollin 2 to 5 mg.^{23,26}

Freed and associates²⁷ have also tested the therapeutic effectiveness of a natural estrogen which is administered by mouth. This preparation, called Premarin, is an extract containing the sulfate conjugated estrogens found in pregnant mare's urine which probably has the same proportion of estrogens as the non-crystalline estrogenic preparation in common use, but whose chief ingredient is estrone sulfate. Using the multiple dosage method with precautions mentioned, they have found that this substance is effective in the daily dosage of 1.25 mg. when administered in 3 doses. A somewhat different method is reported by the same group of workers for parenteral estrogen therapy, using the relief of subjective symptoms of menopausal women as a criterion of effectiveness. The estrogens were administered in substantial dosages at weekly intervals for 3 weeks. Therapy was then stopped and the period of relief from symptoms, taken to indicate the efficiency of the product. Non-specific factors were reduced by having the patients return at regular intervals and placebo injections administered in order to cancel out the psychic factor involved in performing injections. In this manner the authors have tested the potency of a number of estrogens, namely, estrone in aqueous suspension, estrone in oil suspension, diethylstilbestrol dipropionate and diethylstilbestrol dipalmitate.^{24,25,26} By this method they showed that estrone in aqueous suspension was more effective than estrone in oil suspension and on the basis of laboratory investigation have concluded that the aqueous suspension was therefore more effective than estrone in oil solution. The data obtained by the same group of workers with diethylstilbestrol and the esters of this compound likewise demonstrate the greater effectiveness of the dipropionate and dipalmitate over the uncombined estrogen. It was conclusively demonstrated that the dipalmitate is considerably superior to the dipropionate when administered in quantities containing equal amounts of the free compounds. The authors concluded that this again demonstrates the inadequacy of applying laboratory data to human standardization of estrogens, inasmuch as, on the basis of laboratory experiments, the dipropionate should have been superior to the dipalmitate, the minimal effective dose of the former being about one-tenth that of the latter. Furthermore diethylstilbestrol dibenzoate which has a similar action to the dipalmitate in rats is considerably less effective in the human.

Androgens. The most efficient available androgen still remains testosterone propionate. This substance can be administered both hypodermically and in ointments. The compound methyl testosterone has been developed for oral use. Its potency by mouth is about one-third to one-sixth as great as a similar weight of testosterone propionate by injection. In choosing therefore the most desired androgen, the economic factors of each type of therapy must be evaluated, the relative low potency of the oral compound being weighed against the convenience of administration without the need of a visit to the physician. The use of pellets of testosterone or its compounds is the most efficient way of administering androgens. Such preparations, however, are not on the market as yet. Pellet implants produce an effect which acts over long periods of time without

the need of additional therapy. As a rule, 500 to 1000 mg. of testosterone divided into 4 to 5 pellets and implanted appears to be a satisfactory dose. Biskind and his coworkers¹⁰ prefer methyl testosterone pellets because of economy and easier handling in sterilizing the material. For percutaneous administration an effective dosage of testosterone is approximately 15 to 25 mg. daily in an ointment with a lanolin base.

Androgens have been recommended for a number of conditions. There seems to be little doubt that they are satisfactory in replacing the endocrine activity of the testis. Castrate or eunuchoid males may be restored completely to masculinity except for spermatogenic activity. The response of such patients to androgens is well known and need not be described except briefly. The following reactions occur from the administration of androgens to hypogonadal males: increase in blood volume, flushing of the skin and deepening of color, increase in melanin of the skin, growth of the penis associated with sexual activity, stiffening of the beard and an increase in hair growth on the trunk and limbs, genital enlargement, including the skin of the scrotum, a deepening of the voice, and the development of other masculine characteristics. There is also an increase in body weight associated with water retention as well as nitrogen, a slight increase in basal activity, closure of the epiphyseal lines in adolescents, increase in cardiac output, and development of acne. An overdose of androgens may result in the following complications: edema of the lower extremities, bilateral enlargement of the breasts, priapism, precocious maturity in adolescents, and excessive acne. Most of these reactions are reversible and there is a return to the original condition within a few weeks following cessation of therapy. The average dose of testosterone propionate in replacement therapy is about 75 to 150 mg. weekly. Methyl testosterone is usually administered in dosages of 30 to 90 mg. daily. It is claimed that the administration of bile acids enhance the oral effectiveness of the androgens. In addition to treating outspoken cases of testicular failures, androgens have been used in the therapy of functional cryptorchidism. Moderately satisfactory results have been obtained with such therapy, but it appears that the use of chorionic gonadotropin is more effective than androgens.²⁵

Considerable publicity has been given to the use of androgens in the male climacteric.¹⁷ This condition is rather vague because of the lack of criteria for determining the symptoms of this condition and because of the extreme variability in the age at which there is a decline of sex powers in males.²⁶ It is generally thought that hot flashes, nervous irritability and other symptoms characteristic of female menopause are also seen in the male climacteric. It is acknowledged that such symptoms are found only rarely in men. However, a few cases have been reported in which such symptoms are found and these have responded to androgen therapy. There is still inadequate evidence that androgen of any value in senile impotence or in premature impotence without organic cause. There may be temporary benefits which are probably the basis of suggestion. In regard to psychic impotence, Carmichael and Noonan¹¹ find that this substance is of limited value and that the responses are of non-specific nature. Involution melancholia in post-androgen therapy have the same status as estrogen therapy in post-menopausal depression. Pardoll and Behrman¹² showed that androgens increase the bladder function and increased the skin temperature but had no effect on the mentality of such patients. It is of significance that Lusk and others²⁷ have shown that testosterone propionate has a

effect on senile males much the same as it does on younger men who are not castrated. In the treatment of male homosexuality, it has been shown through the use of androgens that little reversal of the sexual tendency is encountered.

The action of testosterone therapy on somatic growth has been shown to be of considerable importance. This work has been developed from the experiments of Dorf, and others, who showed that chorionic gonadotropin therapy in young boys resulted in an increase in skeletal development. This effect is believed to result from androgen liberation of the testes. Androgen therapy has an effect on epiphyseal closure but nevertheless it has a powerful effect on causing bone growth under certain conditions.^{53,70} Finkler and others²⁰ have shown that androgen therapy in hypogonadal boys produces a significant growth increment. Kenyon⁴² and associates have suggested that this growth may be related to the retention of protein generally throughout the body.

Walker⁶⁸ and others^{38,45} have demonstrated that androgen therapy may be of value in the treatment of angina pectoris. It has been claimed that such therapy induces a drop in blood pressure where there is hypertension. The ability to perform more work without chest pain and a greater sense of well-being results. Many of these patients who were benefited showed definite changes in the electrocardiogram. Nevertheless, although Goldman and Markham³¹ have obtained beneficial results in treating climacteric males with angina, they concluded that their cases could be considered to have the effort syndrome and that there were no actual cardiac lesions. The effect of the androgens in causing an increase in hemoglobin, stability of the peripheral vascular system as well as the psychogenic control of the cardiovascular apparatus may well play rôles in the relief from anginal pain. Testosterone may be of some benefit in renal disease since it has been demonstrated that testosterone neutralizes the action of certain kidney poisons, and increases the survival of animals whose ureters have been ligated.⁶³

Albright, Parson and Bloomberg³ have obtained dramatic results in the androgen therapy of Cushing's disease or adrenocortical hyperactivity. There was in such patients a return of muscular strength, increase in weight, decrease in redness and bruisability of the skin, and a feeling of well-being. These changes were associated with a retention of nitrogen, phosphorus and calcium. Estrogens were ineffectual while progesterone was only of slight value in these cases.

Androgen therapy in hypertrophy of the prostate was received with enthusiasm at first with claims of subjective improvement and relief from bladder discomfort. More recent investigations have discounted the value of this therapy and others have questioned the wisdom of delaying surgery by such a procedure. Even though there may be an apparent improvement, the prostatic hypertrophy is actually not reduced. Where bladder discomfort is due to an atrophic prostate, androgen therapy may afford temporary relief.

The androgens have been used widely in the treatment of gynecologic conditions. This has been reported by a number of workers.^{23,59} The chief danger in such therapy is the induction of virilism in women who have received excessive amounts. The androgens have been reported of value in treating functional bleeding as well as bleeding associated with fibroids. Testosterone propionate, 250 to 400 mg., is capable of completely suppressing a menstrual period. Lesser amounts delay the onset of menses. The exact mechanism of this response has not been established. It has been

postulated that the androgens may either neutralize the estrogen output of the ovaries or inhibit the anterior lobe gonadotropin secretion which controls ovarian activity. Similarly, patients with dysmenorrhea have derived some benefits from androgen therapy. Injections of 150 to 400 mg. of testosterone throughout the month are necessary to relieve this condition. Greenblatt²² has reported that androgens are able to stimulate the libido in women who are frigid as well as to increase the libido in normal women. Greenblatt recommends the implantation of pellets for gynecologic conditions. He has also reported that certain conditions of bladder dysfunction with frequency and incontinence may be dramatically relieved with androgens. These women usually had fibroid tumors of the uterus but apparently the effect of the steroid could not be attributed to decrease in size of the tumor. He believes that the genito-urinary tract is under the influence of hormones which may also account for the changes in these tissues found in pregnancy. Androgens have also been recommended for the treatment of menopausal symptoms where estrogens are contraindicated as in cases in which there is a personal or familial history of mammary cancer. Other gynecologic conditions which have responded to androgen therapy include painful breasts due to chronic cystic mastitis, premenstrual tension, afterpains and suppression of lactation. Attempts to reduce the size of fibroids have been partially successful but of doubtful practicability.

As a rule androgen therapy for gynecologic conditions is most efficient in the hands of specialists.

Hamilton²⁷ discussed in detail the rôle of androgens in acute. The therapy of this condition from the standpoint of endocrines is not yet established.

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RADIOLOGY

UNDER THE CHARGE OF

HARRY M. WEBER, M.D., AND DAVID G. PUGH, M.D.

SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

ANGIOCARDIOGRAPHY

BY HARRY M. WEBER, M.D.

ROCHESTER, MINN.

THAT Roentgen rays would one day prove to be of immense value in the study of the heart and of the circulation seems to have been appreciated since the very beginning of the Roentgen era. Holzknecht was able to bring out a report concerning his observations on the heart in health and disease as early as 1901, 6 years after Roentgen announced the discovery of the type of radiation now bearing his name. A considerable

body of knowledge and experience has been accumulated down the intervening years, and for many years the roentgenologic method has been regarded as an important, even an indispensable, part of the routine clinical study of the heart and great vessels of the thorax. Even among clinical cardiologists it ranks in value immediately after the history and the physical and electrocardiographic examinations. While it is true that certain normal and abnormal conditions of the heart and great thoracic vessels can be determined with accuracy and precision during life only with the use of roentgenologic methods, and that certain others are determined more accurately and with greater facility with these methods than with others, it must be accepted that, as with electrocardiography, there are important cardiovascular abnormalities which exhibit no roentgenologic evidence of their existence at all. Some of these are too small or too new to produce demonstrable changes in the general configuration of the cardiovascular silhouette; and changes in the muscular activity, if present at all, are so minor as to escape even the most refined methods of roentgenologic detection. For the most part, too, the roentgenologic diagnostic elements of cardiovascular disease are not direct, but indirect and inferential in character. Roentgenologic cardiovascular diagnosis is largely a deductive process, the observer using such anatomic changes as enlargement or deformity of the whole or some portion of the cardiac and vascular shadows, abnormality of cardiovascular pulsation, and displacement or distortion of neighboring or contiguous anatomic structures as the premises for his diagnostic deductions. This is because the image of the heart obtained by conventional roentgenoscopic and roentgenographic technique is a composite one and not always analyzable with certainty; and, although the aorta can usually be visualized fairly well, the other large vessels of the thorax are seen but indistinctly when seen at all. The roentgenologic method applied to the diagnosis of other tubular and sacular viscera has been rewarded with greater diagnostic success. This appears to be chiefly because it has been possible to enhance their roentgenologic contrast with the use of radiopaque substances to opacify* them, on the one hand, or with the use of innocuous gases to make them more radiolucent than the surrounding tissues, on the other. The diagnostic yield of the roentgenologic method applied to the alimentary and urinary tracts, and to the respiratory and central nervous systems may truthfully be said to be the greater the easier it is to apply contrast roentgenography and roentgenoscopy to them. Until relatively recent times, no practical way of visualizing the heart and great thoracic vessels had been evolved.

parts of the heart would be very short, especially for its arrival in the superior vena cava, the right cardiac chambers and the pulmonary vessels, but the interval, in most instances, would also be quite constant. It could be shown, too, that a longer and more variable period of time would be required for the injected contrast solution to reach the left cardiac chambers and the thoracic aorta. Accurate estimation of these intervals had to be made, and for this purpose Robb and Steinberg⁵ made practical use of the methods of Hitzig³ and of Robb and Weiss⁹ of determining the circulation times between the arm and pulmonary capillaries and between the arm and the carotid sinus respectively. They found that the superior vena cava, its larger tributaries, and the right atrium were radiopaque in $1\frac{1}{2}$ seconds after the beginning of the injection, the right ventricle and the pulmonary arteries in about 3 seconds, the pulmonary veins and the left atrium in from 6 to 8 seconds, while it took from 8 to 10 seconds for the contrast solution to reach the left ventricle and the aorta. The position of the patient in relation to the Roentgen ray tube and film also had to be determined before injection was begun, and it would vary, of course, with the structures the observers wished to visualize. This posing was done under roentgenoscopic control. In their original work, Robb and Steinberg used an ordinary stereoscopic cassette changer to obtain 2 roentgenograms in rapid succession. They were able to make visible the right side of the heart and the pulmonary arteries practically every time they tried to do so, but they were not quite so consistently successful in obtaining a satisfactory visualization of the left chambers of the heart and the aorta.

They used the contrast substance diodrast (3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine), which contains 49.8% of iodine. It was prepared in 70% solution. It was found to be the most satisfactory of all available similar drugs, because it mixes freely with the blood, is eliminated quickly, is inert, is relatively non-toxic, and is non-irritating except rarely at the site of injection in a few cases. Other radiopaque substances like skioldan (an iodomethane sulfonate of sodium) and hippuran (a sodium salt of ortho-iodo-hippuric acid) also were given consideration, but they were found to cause unfavorable reactions when administered in sufficient quantity and concentration. The dose of the radiopaque drug had to be varied to some extent with the size and weight of the patient and also with the part that the observer wished to visualize. As the observations were extended, it was found that while a 70% concentration was the most satisfactory for all purposes, concentrations as low as 40% could be used for opacifying the superior vena cava, the right side of the heart, and the pulmonary vessels. The injection was made into an antecubital vein, and had to be made rapidly. Robb and Steinberg procured a special transfusion needle with an exceptionally large bore to increase the speed of injection. They found that in the average case 35 cc. of the 70% solution (24.5 gm. of diodrast) was needed to opacify the left chambers of the heart and the thoracic aorta, and 25 to 30 cc., to visualize the pulmonary blood-vessels. For subjects with a large thick thorax, or with cardiac enlargement, or with pulmonary congestion, larger quantities were found to be necessary. The dose was found to vary between 25 and 45 cc. of the 70% solution. The solution must be injected in 2 seconds or less, and this rate of injection seemed to cause little difficulty in the average case. In general, the immediate reaction of patients to the injection was mild and transient even in cases in which the patients were quite ill, and there were no serious delayed effects. No fatality or other serious consequence was experienced.

These are the fundamental aspects of angiocardiology. Robb and Steinberg,^{6,7} the originators of the method, described in two articles the technique of injection and of roentgenography in minute detail, outlined precautions to be observed, and indicated the contraindications to the use of the method. These papers are required reading for anyone who wishes to make practical use of the method.

Apparently, the outstanding technical difficulty attending practical application of angiocardiology is that of establishing the precise interval when roentgenographic exposures are to be made after injection of the contrast solution has been begun. Sussman, Steinberg and Grishman⁸ have called particular attention to this point. They suggested the use of the conventional radiographic polygraph with which multiple exposures can be made on a single film as rapidly as the polygraph tray can be shifted. They also suggested that theoretically, at least, the best angiocardiology method would be a motion picture of the roentgenoscopic screen made continuously while the opaque blood was passing through the cardiovascular and pulmonary circuits. They tried this with success, as Stewart and his associates¹⁴ also had done. This procedure, however, had the practically insuperable disadvantage of demanding a special and very expensive high-speed photographic lens, not generally available. Another objectionable feature lay in the circumstance that a very rapid and sensitive, therefore, coarsely grained photographic emulsion was required, and this brought with it too much loss of photographic detail. As a compromise, Sussman and his associates¹⁵ tried and recommended the use of a "still" camera equipped to make multiple exposures of the roentgenoscopic screen in rapid succession. Using a commercially available roentgenoscopic screen and photographic film, f1.5 or f2 camera lenses, and a rotating target Roentgen ray tube, these observers found that a minimum of 10 exposures could be made during a period of observation extending over 8 seconds. In this way it became possible to get as many as 16 exposures in the 8 or 10 second interval during which the contrast solution was passing through the cardiovascular and pulmonary circuits, instead of 2 at the most 4 when cassettes were used. No longer was it necessary to calculate the circulation time except when there was reason to suspect considerable prolongation. The roentgenoscopic screen could be observed during the actual time of photography so that exposures could be timed until part or all of the circuit was completed, and the patient could be posed under direct vision. The cost of the apparatus was relatively small, that of the photographic film negligible.

A disadvantage arose, however, in connection with this approach. This time it had to do with the coarse grain of the roentgenoscopic film recorded on the photographic film—especially disturbing when the film was projected or magnified. Direct roentgenography with the rapidity of exposure would be advantageous in many ways, the investigators thought, particularly to visualize small structures of light densities. Sussman, Steinberg and Grishman¹⁶ soon were instrumental in having ingenious apparatus designed and constructed with which 8 direct roentgenograms of excellent quality could be produced in the short interval time required for angiocardiology. It was a wooden wheel 14.2 inch (36.1 cm.) in diameter, mounted on an axle, and carrying eight 10 by 12 inch (25.4 by 30.4 cm.) cassettes mounted on its periphery. The wheel is rotated manually behind a screen of lead provided with a 10 by 12 inch (25.4 by 30.4 cm.) in size, behind which is a lead apron. A door stop holds the wheel as each cassette arrives at

behind the aperture in the screen of lead. The patient is posed beforehand by roentgenoscopy, one cassette being removed and replaced by a fluorescent screen. The inventors of this device visualized mechanical improvements which would make automatic rotation and automatic exposure possible. In this way, errors inevitably attending hand operation could be eliminated, and the 8 exposures could be obtained in a shorter and still more advantageous period of time. Schwarzschild¹⁰ regarded the apparatus just described as large and unwieldy, so he set about devising another which he claimed had the advantage of greater ease of operation, diminished requirements of space, and a mounting which made it possible to adjust the apparatus for height, a convenience which the apparatus of Sussman and his associates did not seem to possess. Essentially it is a rectangular box divided into 3 compartments in line. One of the compartments receives the unexposed cassettes, in the second the cassettes are exposed, and the third receives them after exposure. A fluorescent screen is mounted in the second compartment so that the patient can be posed under roentgenoscopic control. The cassettes are shifted from one compartment to the others by means of a thrust bar, connected electrically with the Roentgen ray timer, and the arrangement is such that when the thrust bar is withdrawn the timer circuit is closed and the exposure is made. A device is also incorporated in the apparatus by means of which the time of exposure is recorded on each film. According to the designer, 7 exposures in 6 seconds can be made with this machine without difficulty, and it is anticipated that a greater number will be possible with more finished construction. Thus it is apparent that as time goes on the technical handicaps of angiocardiology are being overcome one by one, and the result is sure to be a more general use of the method and a more profound appreciation of its diagnostic potentialities.

What has been the diagnostic yield of angiocardiology so far? The originators could foresee that an important practical application would be found in the study of congenital disease of the heart, and they were the first to make observations on this cardiovascular anomaly. Early in their experience with this new method of investigation, they reported that while they had not yet been able to get direct visualization of the abnormal communication in cases of interatrial and interventricular septal defects, or in cases of patent ductus arteriosus, they⁸ did obtain satisfactory indirect evidence of the defect in the first-named disorder and the last, by observing recirculation of the opacified blood, and in the cases of interventricular septal defect by noting selective enlargement of the ventricles and of the pulmonary artery. They also were able to demonstrate, in cases of coarctation of the aorta, the constricting deformity of the aorta and the collateral circulation developed as a result of it.

Grishman, Steinberg and Sussman¹ also published observations on 2 cases of coarctation. In the first case the narrowing in the proximal descending aorta was demonstrable, the aorta immediately above and below the constriction was normal, the left ventricle was dilated and hypertrophied, and the right internal mammary artery was dilated. The clinical findings in this case were typical, but corroborative roentgenologic evidence was lacking without contrast visualization. In the second case, a complicated one, the patient had extreme hypertension, cardiac murmurs, lowered blood pressure in the legs, differences in blood flow in the upper and lower extremities, no evidence of renal disease, and roentgenographically demonstrable notching of the ribs which suggested coarctation. There also were signs of exophthalmic goiter. Angiocardigraphic

examination revealed a constriction of the descending aorta below the exit of the left subclavian artery, marked hypertrophy of the left ventricle, and a dilated supracardiac aorta.

These investigators² also studied a case of the tetralogy of Fallot, and were able to get visual evidence of each one of the classic anatomic features of the syndrome: stenosis of the pulmonary artery, dextroposition of the aorta, interventricular septal defect with right-to-left shunt, and hypertrophy of the left ventricle. Pursuing the study of congenital heart disease, the same observers¹² have published observations on 3 cases of dextrocardia showing how contrast visualization can be made to prove the actual anatomic relationships both in true dextrocardia with *situs inversus* and in the several anatomic varieties of dextroposition of the heart.

Robb and Steinberg⁸ also reported observations made on patients with acquired heart disease. In cases of rheumatic mitral stenosis and insufficiency, they found, among other things, that the prominence of the pulmonary artery in the frontal view was caused not by the enlarged pulmonary conus or the left atrium, but solely by the dilated pulmonary artery, that the exaggerated hilar and pulmonary roentgenographic markings were the shadows of engorged blood-vessels, and that the left auricle formed the convexity immediately below the pulmonary arch. In syphilitic aortitis it was possible to make visible the infracardiac portion of the aorta, an observation heretofore impossible to make, but important because this portion is the site most frequently involved with syphilitic changes. It was also possible to determine the exact site, size and shape of aortic aneurysms. In hypertensive heart disease it was possible to demonstrate the degree of hypertrophy and dilatation of the left ventricle, the torsion and unfolding of the aorta, "buckling" of the innominate artery, and the left subclavian artery forming the anterior boundary of the "aortic triangle." In arteriosclerotic cardiovascular disease little in the way of cardiac change was demonstrable, but it was possible to show several kinds of pathologic change in the aorta, even when there had been no hypertension, circulatory failure or coronary thrombosis. In one case, the presence of a pericardial effusion was proved beyond reasonable doubt by showing that the cardiac chambers were within normal limits of size in a cardiac silhouette markedly increased in size.

In cardiovascular changes existing in various chronic pulmonary diseases, such as pulmonary tuberculosis, bronchiectasis, bullous and generalized emphysema, and primary carcinoma of the bronchus, Robb and Steinberg⁸ elicited evidences of pathologic change that were both interesting and important. They concluded that the greatest value of aortic radiography in this field was in disorders near the hilum, which often cause great diagnostic difficulties. Hilar masses, they said, can be distinguished from the neighboring blood-vessels, and their site and configuration determined from the vascular compression and displacement they produce. Steinberg, Robb and Roche¹³ were able to demonstrate the value of the method for this purpose very vividly.

and roentgenologic examination of the thorax or the electrocardiographic examination give evidence of enlargement of the right side of the heart, although it should be noted that it is notoriously difficult to detect minor degrees of enlargement of the right side of the heart in the teleoroentgenogram. In 2 of the cases, both with marked emphysema of long duration, there was no right ventricular dilatation, and Sussman and his associates offered no explanation of this finding. The angiocardigraphic findings were also correlated with the electrocardiographic findings, and in 13 of the 24 cases of definite or probable enlargement of the right ventricle the electrocardiogram was normal. The lack of right axis deviation in some of the cases was assumed to be due to the coincidental presence of left ventricular enlargement resulting from some other type of heart disease. Finally, Steinberg and his associates¹¹ applied the angiocardigraphic technique to the study of a case of arteriovenous fistula involving the third portion of the left subclavian artery, and they said that the procedure is especially well suited for localizing arteriovenous fistulas involving the large vessels near the heart.

Contrast visualization of the heart is undoubtedly here to stay. It has already made important contributions to medical knowledge and there is promise of even more in the future. Although the method is safe and practical, it is one that demands a high degree of teamwork and a great precision in technique. It will be most productive of good diagnostic results in the hands of those already well grounded in other methods of cardiovascular diagnosis. Not all patients with cardiovascular disease should be subjected to it, rather let it be reserved for those who present unusually difficult diagnostic problems not readily solved by the older and more familiar methods of cardiovascular diagnosis.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 16, 1943

Capillary Permeability to Horse Protein in Burn-shock. MARTIN NETSKY and SAMUEL LEITER (Harrison Department of Surgical Research Schools of Medicine, University of Pennsylvania). The time and rate of

appearance in lymph of intravenously injected horse serum was used as a measure of capillary permeability in dogs. Since the horse serum was injected intravenously, its appearance in lymph represented direct passage across the capillary endothelium. Data obtained on 3 normal and 3 burn-shocked dogs form the basis of this report. Dogs under morphine-barbital anesthesia were closely clipped from feet to axillæ. The cervical lymph ducts and the left thoracic duct were cannulated. Two cc. of horse serum per kilogram of body weight were injected intravenously. The body was then immersed up to the axillæ in water at 72° C. for 60 seconds. The time of appearance and the concentration of horse serum in lymph was determined by precipitin reaction with rabbit anti-horse serum, and the washed precipitate was read turbidimetrically with the Klett-Summerson colorimeter. Protein levels in blood and lymph were determined by the biuret method of Kingsley. In normal animals, it was found that horse serum appeared sooner, at a greater rate, and reached higher levels in thoracic duct than in cervical lymph, thus giving evidence that the thoracic drainage area is more permeable than the cervical drainage area. Following the burn, changes in capillary permeability were noted promptly in both the burned (lower body) as well as the non-burned (head and neck) area. In the normal dog, horse serum appeared in cervical lymph in 50 to 100 minutes. Following the burn, it appeared in 10 to 20 minutes. Similarly, horse serum was detected in thoracic lymph of the normal dog in 20 minutes, whereas it appeared in the burned dog almost immediately following the burn. The shape of the time-concentration curve for horse serum was altered in both areas by the burn. Total lymph protein concentration was not increased during the 3-hour observation period.

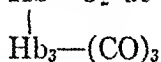
structure in the head or neck, it would seem that in the animals described, the seat of the emetic stimulation and the persistence of the action was a central one; but other interpretations are conceivable (the paper was illustrated by lantern slides and a motion picture of the vomiting in the cat after viscerai deafferentation).

The Effect of Replacement of Normal Blood by Erythrocytes Saturated With Carbon Monoxide. DAVID L. DRABKIN, FREDERIC H. LEWEY, SAMUEL BELLET and WILLIAM H. EHRLICH (Departments of Physiological Chemistry, Neurosurgery, Cardiology, and Pathology, University of Pennsylvania). In one group of dogs severe carbon monoxide poisoning was produced by inhalation of sufficient carbon monoxide to reach "critical" levels of 75% HbCO. After a certain length of exposure under these conditions the animals collapsed with evidence of cardiac and respiratory failure. In those animals which survived extensive necrotic changes were found in the brain (cortex) and heart.

In another group of dogs, levels of 75% HbCO were obtained by replacement of the blood with washed erythrocytes saturated with carbon monoxide (96% HbCO). In these animals no signs characteristic of anoxia (R-T elevation in the electrocardiogram, slowing of conduction, and heart-block) were observed. Necropsy revealed no evidence of myocardial or cerebral damage. Following termination of the transfusion of HbCO containing cells, the percentage of carbon monoxide in the blood decreased approximately 2 times more rapidly than in the dogs poisoned through the respiratory route.

Except for the similar percentage of HbCO in the blood, the two experimental states differ markedly. The partial pressure of carbon monoxide to which the tissues are exposed is very probably greater in the dogs which inhaled the gas. The undetermined factor of tissue poisoning may therefore be operative to a far greater extent in the animals severely poisoned through the respiration.

A more obvious explanation of the results may be the operation *in vivo* of the Haldane and Stadie and Martin effect, previously established *in vitro*. This effect may be described as follows: Partial poisoning of the four iron atom hemoglobin molecule with carbon monoxide results in molecular species which hold the remaining oxygen more tightly. This induced greater affinity, for oxygen decreases the "oxygen unloading capacity" at the tissues. From the dissociation curves of non-poisoned $\text{Hb}_4(\text{O}_2)_4$ and 75% poisoned $\text{Hb}-\text{O}_2$ at 10 mm. pO_2 , it is calculated that the



"functional" hemoglobin (upon the basis of normal unloading capacity) in the latter case is not 25% but only 11%. This presents a clearer view of the meaning of the "critical" level of 75% HbCO in the animals which inhaled the gas. On the other hand, in the transfused dogs a state approaching 75% of $\text{Hb}_4(\text{CO})_4$ and 25% of "functional" $\text{Hb}_4(\text{O}_2)_4$ was attained. Opportunity for appreciable equilibration of the unpoisoned $\text{Hb}_4(\text{O}_2)_4$ as the carbon monoxide dissociated *in vivo* from the $\text{Hb}_4(\text{CO})_4$ was not afforded due to opposing rates of rapid "blowing off" of CO in the lungs and relatively slow uptake of CO by the hemoglobin. The element of time here operates presumably in such a way that the pCO built up in the plasma is appreciably lower than in dogs poisoned through the respiratory route.

The much more rapid decrease of HbCO in the blood of the transfused animals is also explainable by the operation *in vivo* of the Haldane effect.

It may be added that the transfusion of the HbCO containing cells often prevented imminent circulatory failure attendant upon the severe bleeding procedure in the "replacement" experiments. These studies have suggested the probable value of prompt transfusion of normal blood in dogs severely poisoned through the inhalation of carbon monoxide. Transfusion of normal blood has been tested, and found effective under appropriate conditions.

Intravenous Ammonium Chloride for the Treatment of Alkalosis. H. A. ZINTEL, J. E. RHOADS, and I. S. RAVDIN (Harrison Department of Surgical Research, University of Pennsylvania). The need for a more effective parenteral method of correcting alkalosis has arisen with increasing frequency since the introduction of continuous suction drainage in the preoperative preparation of patients with pyloric obstruction. Sodium lactate has been administered intravenously for the correction of acidosis, but no preparation has been generally available for the parenteral treatment of alkalosis.

Although the kidneys will usually restore the electrolyte pattern of the plasma, if sufficient fluid and salt are provided, there remains an occasional patient who does not respond to this type of therapy. It has been demonstrated that postoperative patients and patients with pneumonia are often unable to excrete excess sodium.

Intravenous ammonium chloride was administered 12 times to patient with severe alkalosis. Although our experience has been too limited to establish firmly the safety of the method, its use is justified when the intravenous administration of sodium chloride and fluid has restored the serum chlorides and total serum base to normal, but has failed to overcome the alkalosis.

No serious reactions have occurred when a 2% ammonium chloride was administered in a 5% glucose solution intravenously. The response to this therapy is quite uniform. One gram of intravenous ammonium chloride reduces the serum CO_2 of an 150 pound adult approximately 1.1 vol.-%.

BOOK REVIEWS AND NOTICES

FIRST AID AND BANDAGING. By ARTHUR D. BELILIOS, M.B., B.S. (LOND.), D.P.H. (ENG.), and others. Pp. 628; 239 figures. Baltimore: Williams & Wilkins Company, 1942. Fourth reprint. Price, \$1.75.

LIKE Hammer's Advanced Handbook, this book is written by English authors who should have had much practical experience in the last few years. It begins with an excellent chapter on General Principles. Consideration of the general structure and functions of the body are condensed into 10 concise and pertinent pages. The 20 pages devoted to the skeleton follow later, just before fracture; and so on with the other body systems. One naturally finds minor differences in terms and procedures from those in use in this country (especially to be regretted is the omission of "the fireman's lift" from the methods of transport by the single helper); but on the whole the book should be warmly recommended. E. K.

MILITARY SURGICAL MANUALS. IV. ORTHOPEDIC SUBJECTS. Prepared and Edited by the Subcommittee on Orthopedic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 306, 79 figures. Philadelphia and London: W. B. Saunders Company, 1942. Price, \$3.00.

THIS volume is the fourth of a series designed to furnish the medical departments of the United States Army and Navy with concise presentations of necessary information in the field of military surgery. Its four sections cover ununited fractures, injuries of the spinal column, compound fractures, and osteomyelitis. In general, its subject material is limited to orthopedic surgery and its military application. No discussion of simple fractures, dislocations (except those of the vertebral column), and sprains is given, and the subject of amputations is only briefly treated. This volume will have only limited application for those not in the armed forces. M. T.

THE VERTEBRATE EYE. By GORDON LYNN WALLS, Research Associate in Ophthalmology, Wayne University College of Medicine. Pp. 785; 197 figures (3 in color), numerous plates and tables. Bloomfield Hills, Mich.: Cranbrook Institute of Science, 1942. Price, \$6.50.

THIS is the most important book on the subject to appear in the last few years. Dr. Walls has indeed knowledge of the comparative morphology of the vertebrate eye and from this he has traced the evolutionary changes which have led to functional specialization throughout the vertebrate series. The book is logically organized into three sections. In the first part the human eye is dealt with and an excellent résumé is given of the physiology of the duplex retina. Most of the recent developments in this field are well recounted, perhaps only lacking in an adequate presentation of the electrical phenomena which accompanies retinal stimulation. The second and third part are comparative morphology and show how various structures in the eyes of the vertebrate series have been developed to meet the needs of the particular animal.

The style is exceedingly readable and the author manages to retain one's interest throughout. Considerable praise should also be given to the publishers for the excellent type and illustrations, the beauty and perfection of which add much to the book's enjoyment. The book cannot be too highly recommended and should be owned by everyone interested in the eye.

F. A.

NASAL MEDICATION—A PRACTICAL GUIDE. By NOAH D. FABRICAN. Pp. 113; 20 illustrations. Baltimore: The Williams & Wilkins Co. 1942. Price, \$2.50.

This book in a condensed form presents the more important facts of anatomy and physiology. Particular stress is placed upon nasal cilia and hydrogen ion concentration of nasal secretions. The best methods and methods of application for both acute and chronic disease are discussed. This work is of decided value to anyone interested in this type of

DISEASES OF THE BREAST. By CHARLES F. GESCHICKTER, M.A., Lieutenant, Commander, Medical Corps, U. S. Naval Reserve, Director, Francis P. Garvan Cancer Research Laboratory, Pathologist, St. Louis Hospital, Baltimore. With a Special Section on Treatment in Collaboration with MURRAY M. CORELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School, Visiting Surgeon and Chief Oncologist, University Hospital, University of Maryland Medical Center, Baltimore. Pp. 829; 593 illustrations. Philadelphia: J. B. Lippincott Company, 1943. Price, \$10.00.

The greater part of this book deals with an analysis of clinical and pathologic data of some patients seen by the author and some from the wards of Johns Hopkins Hospital, and of data collected by Drs. Bleby, Halsted and Welch, and others in the Surgical Pathological Laboratory of Johns Hopkins Hospital.

Over 2500 cases of breast cancers are analyzed, 1200 cases of metaplasia, many benign tumors, and a variety of the rare conditions which affect the breast. There is detailed discussion of the clinical aspect of the disease, analysis of end-results, and of the gross and microscopic changes. There are many excellent illustrations, charts and tables. Often photographs of the patient and the gross specimen and a photomicrograph are used in correlating the pathologic changes with the clinical.

Considerable emphasis is placed on the endocrine factors involved in the etiology and treatment of breast diseases. In this connection are described experiments by the author on the production, by administration of certain substances, of various pathologic changes in the mammary gland of rats. Comparisons are made of these changes with those found in patients. In this is elaborated a theory of how pathologic changes occur in the breast.

The book is essentially a presentation of information derived from the author's personal experience and an expression of personal interpretation placed in relation to the views of others. The book contains a wealth of interesting and useful to both clinicians and pathologists.

cases observed at the Massachusetts General Hospital, the Collis P. Huntington Memorial Hospital, and the Pondville Hospital. No attempt was made to deal with the entire field of neoplasia; but a statistical analysis is presented of 5481 original cases of carcinoma of the skin, breast, mouth, pharynx, larynx, anus, vulva, penis and serotum, of melanoma of the skin, and of some sarcomata. Other cancers were reviewed but not statistically analyzed, the experiences of the authors being correlated with opinions and experiences recorded in the literature.

In the first part of the book the authors discuss the anatomy of the lymphatic drainage areas of the neck, axilla and arm, groin, pelvis and abdomen, and thorax. In the second and main part they present a detailed analysis of the incidence of lymph node metastases in various cancers; a correlation between the incidence of metastases and such characteristics of the original tumor as the size, duration, grade of malignancy, and other clinical manifestations; and last but not least the results obtained with dissection of lymph nodes and their treatment with radiation. In the third and last part the authors describe the operations on various lymph nodes including miscellaneous operative procedures such as biopsy and radium implantation.

The text is clearly written and the material well organized and concisely presented. The book represents an important contribution to the knowledge of cancer and should be equally valuable to the surgeon, radiologist and pathologist, as it is no longer necessary that decisions in regard to the proper management of the regional lymph nodes in neoplasia be made or modified on the basis of tradition, opinion or prejudice. We now have an excellent book which furnishes abundant information as to the likelihood of metastatic involvement, and as to the curability of involved nodes when they are present.

W. E.

LOVE AGAINST HATE. By KARL MENNINGER, M.D., with the collaboration of JEANETTE LYLE MENNINGER. Pp. 311. New York: Harcourt, Brace & Co., 1942. Price, \$3.50.

THIS book presents an interesting discussion of the emotional life written primarily for the layman. The practising physician meets many of the problems which are discussed in it. He will not find much that is essentially new, but will have his own thoughts clarified in the field of the emotional life.

The author rightly points out the failure of patients to consult their physicians on matters of sexual frustration, and, more important still, that physicians generally neglect to investigate them. He correctly states that the teaching of sexuality is still taboo in the medical schools of American universities in spite of the fact that psychiatrists see many dramatic examples in their daily lives which they cannot forget.

The unhappiness which results from sexual frustration plays such an important rôle in life and receives so little attention from physicians, that the reader of this review, if he practises medicine, would do well to not only read but study the volume and others on the same subject.

D. M.

FUNDAMENTALS OF IMMUNOLOGY. By WILLIAM C. BOYD, Ph.D., Associate Professor of Biochemistry, Boston University, School of Medicine; Associate Member, Evans Memorial, Massachusetts Memorial Hospitals, Boston, Mass. Pp. 446; 45 illustrations, 67 tables. New York: Interscience Publishers, Inc., 1943. Price, \$5.50.

THE fundamentals of immunology are presented for the benefit of medical students, chemists, biologists, and others interested in an understanding of the basic principles of the science. The material is aimed at the beginner; but the book will also be useful to the professional immunologist, as the author has used smaller type for material of more interest to the advanced student or professional immunologist. The modern views on a subject are usually

given first, omitting the historical development of a subject in order to serve space; but the author is not dogmatic and discusses controversial points. The book has a well-organized table of contents, a good index, and a list of references appended to each chapter. The emphasis is on serology. The chapter, comprising 88 pages (about one-fifth of the book) is devoted to laboratory and clinical techniques employed in the field of immunology. The subject matter is presented very clearly and concisely and printed in a practical style. It is a book which every student of medicine will want to read to bring his knowledge up to date in a field which is being actively worked. H. M.

EMOTIONS AND MEMORY. By DAVID RAPAPORT, Ph.D., Head of the Department of Psychology, The Menninger Clinic, Topeka, Kan. Foreword by FRANK FREMONT-SMITH, M.D. Pp. 282. Baltimore: The Williams & Wilkins Company, 1942. Price, \$3.00.

IN disorders wherein the emotional element has been potent, repression, distortion or displacement have usually occurred, thus rendering the emotionally charged memories unavailable to the examining physician. In this monograph the writer has scrutinized the literature of psychology, psychopathology and psychoanalysis, to determine the relationship between emotions and remembering; doing so has led him to suggest a new theory of memory function: "... the memory laws based on logical 'meaning' and 'organization' of the memory material refer only to special cases of memory organization; the more general theory of memory is the theory based on 'emotional organization' of memories—in other words, on the organization of memory strivings."

The chapter on Contributions of Psychoanalysis speaks of the "whole-forgetting of childhood memories," ... as "an amnesia determined by the inhibition imposed on the evolving infantile sexuality." Direct Experimental Evidence includes a brief but lucid account of the important Rorschach Test. Under Contributions of Hypnosis, the discussion of drugs is too scant, although mention is made of marijuana which often causes its votaries to recall the long forgotten. The bibliography of this stimulating contribution to psychology is immense. S. V.

microscopic anatomy, pathology and physiology of the ovary. The author has based his studies on over 1100 cases of benign and malignant tumors of the ovary. In addition he has incorporated the findings and opinions of many other contributors in this field, supplying thereby an extensive bibliographic list at the end of each chapter. "Not only are the anatomy and physiology of ovarian neoplasms discussed, but an attempt has been made to explain the basis of the symptoms. Association of ovarian neoplasms with other conditions such as pregnancy, and the procedure and care in such cases have been elaborated. Necessarily, new points of view dealing with the origin, classification, and . . . of ovarian tumors have been expressed, since progress in . . . past fifteen years has been so great." The material is well illustrated with both gross and many fine microscopic photographs. This book should be of definite value to all interested in this phase of medicine.

M. T.

A SURGEON'S FIGHT TO REBUILD MEN—AN AUTOBIOGRAPHY. By FRED H. ALBEE, M.D., F.A.C.S., F.I.C.S. Foreword by LOWELL THOMAS. Pp. 349; 11 illustrations. New York: E. P. Dutton & Co., Inc., 1943. Price, \$3.50.

In this volume, written primarily for lay readers, a distinguished pioneer in the field of bone graft surgery presents a readable and popular review of his career. In reading the book one gains the impression that the scientifically creative period of the author's life was concentrated in the years before the first World War. It was during this period that he first applied to bone repair the principles of tree-grafting which he had learned from his grandfather on a Maine farm. In illustrated appendices the author shows in interesting fashion the many applications of the principles of the joiner's art to orthopedic surgery. The middle section of the book is devoted to the organization and operation of the U. S. General Hospital No. 3, in which the author played an important part during World War I. Another outlet for the apparently boundless energy of the writer has been the program of rehabilitation of individuals disabled through industrial injuries, particularly in the state of New Jersey. In more recent years, however, the author's interest has become more and more focused on the development of a private sanitarium in Florida, a project which from the standpoint of scientific medicine is in decided contrast to the author's earlier contributions. The faith which the author expresses in "vitaminization and mineralization" as a "cure-all" for a variety of diseases is something of a departure from his early scientific research. Dr. Albee has filled a rôle of an international medical diplomat through his interest in international societies of surgery and orthopedics and has cultivated a wide acquaintance, particularly in South and Central America, through extensive travel abroad. In writing this book he has perhaps succeeded in carrying out his principal aim, but has not, in the Reviewer's opinion, made a noteworthy contribution to literature, medical or otherwise.

J. L.

INDIGESTION. ITS DIAGNOSIS AND MANAGEMENT. By MARTIN E. REHFUSS, Professor of Clinical Medicine, and SUTHERLAND M. PREVOST, Lecturer in Therapeutics, Jefferson Medical College, Philadelphia. Pp. 556; 35 tables; 63 figures. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$7.00.

In this book, a well-known gastroenterologist presents his personal views on the subjects that are regarded as of clinical importance in connection with the syndrome of indigestion. He discusses somewhat informally the various types of digestive disturbance, their causes, the means available for their recognition and the procedures which he employs for their management. Although allegedly written for the guidance of the busy practitioner, many aspects of the subject, especially gastric analysis and therapy, in which the author has special interest, are covered in great and perhaps unnecessary

detail. In addition to a discussion of diet throughout the book, 170 pages are devoted entirely to that phase of treatment. The book is cursive but practical, simple in outline but somewhat confused in its details. Some condensation would render it more helpful to the clinician; but it is easily readable, contains many important clinical observations and points to a subject that deserves special emphasis at this time when the war has attracted attention on diseases of the digestive tract. The illustrations are excellent. T

MODERN TREATMENT OF VENEREAL DISEASES. By F. T. BURKE, M. B., Ch.B. (Glas.), Lieut. Col. (late), Royal Army Medical Corps; formerly Director of the London County Council (Whitechapel) Clinic; formerly Venereologist in the Public Health Department of the London County Council, etc. Pp. 105; 4 figures, many tables. London: John Bale, 1942. Price, 12/6d.

THIS book is based on the author's wide experience with venereal diseases that he acquired in the British Army and in venereal disease clinics, especially that of Whitechapel, the largest in England. Col. Burke who died over 10 years ago, represented characteristic British caution in the use of new remedies. Though his work was brilliant in his day and his mind open to a critic, he was not open to new ideas, developments in the field of venereal diseases have been so rapid that this posthumous publication appears to experts in the field as a little out of date in a number of items in the treatment of syphilis and gonorrhoea. One question, then, the desirability of publication at this time, when so much more adequate treatment, if it has been demonstrated to be really adequate, is especially important. L.

THE SIGHT SAVER. By C. J. GELLING. Pp. 202; frontispiece. New York: Harvest House, 1943. Price, \$2.00.

THIS book brings to the layman reliable answers to all questions he may have about the normal eye and its most common ailments. The book is a guide of dealing with non-medical eye practitioners is rightfully repeated. Self-treatment, proprietary drugs, and quackery are dealt with in a straightforward manner as to leave no doubt as to their status. The material is, with minor exceptions, quite accurate. The disadvantage of much repetition in these 200 pages is offset by its encyclopedic arrangement which makes it a valuable reference. P

- Vascular Spasm.* By ALEXANDER JOHN NEDZEL, M.D., M.S., Associate Professor of Pathology. Pp. 151; 161 figs. Urbana: University of Illinois Press, 1943. Price, \$2.75 clothbound, \$2.25 paperbound.
- Principles and Practice of War Surgery.* By J. TRUETA, M.D., Formerly Director of Surgery, General Hospital of Catalonia, University of Barcelona; Assistant Surgeon (E.M.S.), Wingfield-Morris Orthopaedic Hospital, Oxford; Acting Surgeon-in-Charge, Accident Service, Radcliffe Infirmary, Oxford. Introduction by OWEN H. WANGENSTEEN, M.D., Minneapolis, Minn. Pp. 441; 144 illus. St. Louis: C. V. Mosby Company, 1943. Price, \$6.50.
- Chemotherapy of Gonococcic Infections.* By RUSSELL D. HERROLD, B.S., M.D. Pp. 140; a few tables. St. Louis: C. V. Mosby Company, 1943. Price, \$3.00.
- Endoscopic Prostatic Surgery.* By ROGER W. BARNES, M.S., M.D., F.A.C.S., Professor of Clinical Urology, College of Medical Evangelists; Chief of Urology Service, White Memorial Hospital and Out-Patient Clinic; Senior Attending Surgeon, Los Angeles County Hospital; etc. Pp. 235; 104 illus. St. Louis: C. V. Mosby Company, 1943. Price, \$6.00.
- Behind the Sulfa Drugs. A Short History of Chemotherapy.* By IAGO GLADSTON, M.D. Preface by PERRIN H. LONG, M.D. Pp. 174. New York: D. Appleton-Century Company, Inc., 1943. Price, \$2.00.
- Proteins, Amino Acids and Peptides as Ions and Dipolar Ions.* By EDWIN J. COHN and JOHN T. EDSALL, Harvard Medical School. Including Chapters by JOHN G. KIRKWOOD, Cornell University, HANS MUELLER, Massachusetts Institute of Technology, J. L. ONCLEY, Harvard Medical School, GEORGE SCATCHARD, Massachusetts Institute of Technology. Pp. 686; many tables and figs. New York: Reinhold Publishing Corp., 1943. Price, \$13.00.
- Introduction to Organic and Biological Chemistry.* By L. EARLE ARNOW, Ph.D., M.D., Director of Biochemical Research, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Pa.; Formerly Assistant Professor of Physiological Chemistry, University of Minnesota Medical School, and HENRY C. RERTZ, Ph.D., Assistant Chemist in the Western Regional Research Laboratory, U. S. Department of Agriculture, Albany, Calif.; Formerly Assistant Professor of Agricultural Biochemistry, University of Minnesota. Pp. 736; 90 figs., many tables. St. Louis: C. V. Mosby Company, 1943. Price, \$4.25.
- Flying Men and Medicine.* By E. OSMUN BARR, M.D. Pp. 254; 8 figs. (1 colored plate). New York and London: Funk & Wagnalls Company, 1943. Price, \$2.50.
- Family Treasures.* By DAVID D. WHITNEY, Ph.D., Professor of Zoölogy, University of Nebraska. Pp. 299; 234 figs. and some tables. Lancaster, Pa.: The Jacques Cattell Press, 1943. Price, \$3.50.
- Operating Room Technique.* By EDYTHE LOUISE ALEXANDER, R.N., Supervisor of the Operating Rooms of The Roosevelt Hospital, New York; Formerly Supervisor of Operating Rooms, Mountinside Hospital, Montclair, N. J.; Supervisor of Private Pavilion Operating Rooms, New York Hospital. Pp. 392; 221 illus. St. Louis: C. V. Mosby Company, 1943. Price, \$3.75.
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NEW EDITIONS

Various Gases and the Principles of Respiration Influencing Their Action. By YANDELL HENDERSON and HOWARD W. HAGGARD, from the Laboratory of Applied Physiology, Yale University. American Chemical Society Monograph Series. Second ed. Pp. 294; various tables. New York, Reinhold Publishing Corp., 1943. Price, \$3.50.

Diseases of the Nose, Throat and Ear. By WILLIAM L. BALLENGER, M.D., F.A.C.S., Late Professor and Head of the Department of Otolaryngology, Rhinology and Laryngology, School of Medicine, University of Illinois; and HOWARD C. BALLENGER, M.D., F.A.C.S., Associate Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital. Eighth ed. Pp. 975, 160 illustrations, 27 plates (25 in color). Philadelphia: Lea & Febiger, 1943. Price, \$12.00.

Clinical Diagnosis. By JAMES C. TODD, Ph.D., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine; and ALBERT HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation), Head of Division on Clinical Laboratories, Mayo Clinic. Tenth ed. Pp. 911; 380 illus. (32 in color). Philadelphia and London: W. B. Saunders Company, 1943. Price, \$6.00.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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ORIGINAL ARTICLES

PNEUMONIA DUE TO THE STREPTOCOCCUS VIRIDANS*

BY SAUL SOLOMON, M.D.

AND

MENASCH KALKSTEIN, M.D.

NEW YORK, N. Y.

(From the Fourth Medical Division of Bellevue Hospital,
Dr. Charles H. Nammack, Director)

THE *Streptococcus viridans* (*Streptococcus alpha*) has up to the present time received little consideration as an etiologic agent in the causation of pneumonia. Careful search through the literature reveals few reports of cases. The relationship of *S. viridans* to subacute bacterial endocarditis is well established. However, when the organism is found in the sputum of pneumonia patients, it is usually considered as either an upper respiratory saprophyte or a laboratory contaminant. It is our impression that in certain instances, the *S. viridans* is the primary cause of pneumonia and in other cases it may play an important rôle as a secondary invader in pneumococcal pneumonia. From the pulmonary focus, it may occasionally invade the blood stream.⁹

The rôle of this organism in the production of pneumonia suggested itself to us during the observation of 2 pneumonia patients who failed to show the usual good response to sulfapyridine therapy and in whom after careful study, it was found that the *S. viridans* was the causative agent. This report concerns 5 cases of pneumonia attributed to the *S. viridans*.† The disease is relatively rare, but this does not diminish the importance of its recognition.

Following are the protocols of the 5 cases which have come under our observation:

Case Histories. CASE 1. W. H., white male, age 82, suffered from a chest cold for 3 weeks with cough and expectoration of thick gray sputum. He com-

* These cases were studied as part of an investigation concerning the merits of chemotherapy and combined chemotherapy and serum in the treatment of pneumonia, under the auspices of a Committee for Pneumonia Investigation consisting of Drs. Russell L. Cecil, I. Ogden Woodruff, Asa L. Lincoln and Charles H. Nammack (the latter three, directors of the First, Second and Fourth Medical Divisions, respectively), Norman Plummer, Herbert K. Ensworth, James Lieberman, William H. Kammerer and the authors.

† We observed 5 cases of pneumococcal pneumonia whose illness was prolonged by reason of secondary invasion of the infected lung or pleura with this organism.

plained of pain in the left chest, chills, and weakness 5 days before admission. On admission he appeared acutely ill, dehydrated, and dyspneic. There was dullness and bronchial breathing with numerous crepitant rales over the right lower and right middle lobes, and a friction rub was heard in the right axilla. The heart was rapid but not enlarged and no murmurs were heard. No petechiae were seen and the spleen was not palpable. The white cells on admission numbered 15,700 with 64% young forms of polymorphs, 30% mature forms, 3% monocytes and 3% lymphocytes.

The patient's downhill course was rapid. The temperature was 101.6° F. on admission. It soon rose to 105° and remained around 103° until his death 3 days after he was hospitalized. The sputum was thick, gray and mucoid. Sputum studies on admission and on the following day revealed a pure culture of *S. viridans* (alpha). The blood culture yielded a heavy growth of *S. viridans*. Signs of fluid developed at the right base and a thoracentesis 24 hours before death revealed turbid fluid which also showed a pure growth of *S. viridans*. Permission was not obtained for autopsy.

CASE 2. W. M. P., a colored, obese female, age 20 who 2 days following a tooth extraction complained of very severe chest pain and dry cough. She was admitted on the 4th day of illness appearing dyspneic and acutely ill with consolidation of the right lower lobe. The heart was normal on repeated examinations. The sputum culture showed *S. viridans* and a few colonies of Type XVII pneumococci. In view of the fact that alternate cases of pneumococcal pneumonia during this season were treated with serum as well as sulfapyridine as part of a controlled study,² she received 100,000 units of Type XVII antipneumococcal rabbit serum intravenously with no result. A lung suction on the following day showed a pure culture of *S. viridans*.

The patient received 2 gm. of sulfapyridine immediately on admission followed by 1 gm. every 4 hours for 2 weeks with no improvement, although the level of free sulfapyridine in the blood remained about 5 mg. per 100 cc. The temperature ranged about 102° to 103° and the patient's chief complaint was severe chest pain. The physical signs were those of fluid accumulation, consolidation and this was confirmed by a Roentgen ray taken on the 13th day of illness. A thoracentesis, however, yielded only 10 cc. of bloody fluid. The culture showed *S. viridans*. The sputum which had been mucoid and tenacious became bloody and mucoid but never foul. Sputum culture was repeated on the 6th day and showed *S. viridans* in pure culture.

The white cells numbered 13,400 with 70% polymorphs and 10% monocytes on admission but after 2 weeks, the white cell dropped to 11,000 with 50% polymorphs.

Blood cultures were persistently negative. The patient remained toxic, anorectic and febrile. She had a hemoptysis on the 20th day, following which occurred pulmonary edema and death. Permission for autopsy was refused.

CASE 3. M. T., white male, age 59, who had a 2 week history of sore throat followed by weakness, chills, fever and cough 2 days before admission. Two days before admission he noted difficulty in breathing and pain in the chest. He appeared dyspneic and cyanotic with tachypnea and severe chest pain. There were physical and Roentgen evidence of consolidation of the right lower lobe. Sputum type 2 by the Neufeld method of typing III and IXIII gave same. A sputum culture yielded a pure growth of the organism to the *S. viridans*. For therapy he received 250,000 units of Type XIII antipneumococcal rabbit serum intravenously over a 2 day period. He also received a total of 55 gm. of sulfapyridine over the same period.

The patient died 11 days after admission. Permission for autopsy was refused. Lung tissue received and showed fluid consolidation of the right lower lobe. A sputum study 10 days after admission showed a pure growth of *S. viridans*. The white cells numbered 7,000 with 64% polymorphs, 24% mature forms, 10% monocytes and 2% lymphocytes. The patient's temperature ranged from 101° to 103° and he was toxic and anorectic.

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pleurisy and bronchopneumonia of the left lower lobe. A postmortem culture of the infected lung yielded the *S. viridans*, no pneumococci being found. The exudate in the involved lung was fibrinous and contained a predominance of lymphocytes. The lumina of the bronchioles contained considerable desquamated epithelium and lymphocytes. The mucosa and submucosa was infiltrated with white cells, mainly lymphocytes. The heart showed no abnormalities.

CASE 4. S. L., 52-year-old Chinaman admitted on the 3d day of illness with cough, fever, chills, and severe pain in the right chest. He appeared critically ill, and had consolidation of the right lower lobe. His sputum, was mucoid and thick but not bloody. It was typed both on admission and on 3 occasions subsequently, showing several organisms, viz.: *S. viridans*, and Types II, IX, and XXIX pneumococci.

He received sulfapyridine from the 3d to the 13th day, a total of 42 gm. being given. The temperature fell from 104° to 101° on the 13th day, but apart from this, there was little effect upon the patient's general condition. Type II antipneumococcal rabbit serum was given on the 10th day with no apparent effect. The temperature on the 17th day rose to 104° and the patient had chills. A blood culture taken on the 20th day showed *S. viridans* in the broths.

During the 4th week, the process spread to the left upper lobe. During the same period, thoracentesis of the right pleural cavity done on 2 occasions yielded 150 cc. and 175 cc., respectively, of straw-colored fluid with a specific gravity of 1.015, and a predominance of polynuclear cells in the exudate. Culture of the first specimen yielded *S. viridans*. The second specimen was sterile.

During the 6th week, sulfamethylthiazole was used for 4 days, a total of 16 gm. of the drug being employed with little effect.

The patient ran a prolonged, severe, febrile course. For weeks he was in an exhausted state but eventually he recovered.

CASE 5. P. S., a white miner, age 59, with a history of chronic "asthma" who developed severe chills, pleurisy and fever 6 days before admission. He showed signs of partial consolidation of both lower lobes on admission. His sputum was white, mucoid and yielded Types III, XII, and XXXII pneumococci on typing. On the 24th day, his sputum was bloody. Sulfathiazole therapy was started with no effect, although the blood levels ranged between 7 and 10 mg. per 100 cc. The temperature remained between 101° and 102° until the 20th day, following which it began to fluctuate. The patient was severely toxic. There was no evidence of fluid in the chest. There were no cardiac murmurs, no petechiæ, no hematuria and the spleen was not felt. Roentgen rays showed partial consolidation of both lower lobes as well as fibrosis and emphysema.

The blood cultures, which, during the early stages were sterile, yielded *S. viridans* on the 40th day. This organism was tested by Dr. Whelan D. Sutliff in the laboratory of the New York Board of Health and was found to be resistant to sulfathiazole.

The patient ran a septic downhill course, death occurring on the 50th day of illness. Permission for autopsy was refused.

These cases of *S. viridans* pneumonia demonstrate certain features in common as seen from Table 1. The lesion was lobar with a tendency to spread to involve more than one lobe. This was demonstrated by roentgenograms in the 4 cases where Roentgen rays were taken. A prominent symptom was intense pleural pain. Pleural effusion occurred in 4 of the 5 cases. The fluid was thin and yellow with a predominance of polynuclear leukocytes; and in none of them did it become purulent (empyema). In all 4 cases *S. viridans* was found in pure culture in the fluid. The severity of the clinical course is indicated by the fact that 4 of the 5 patients died. Death occurred on the 8th, 26th, 26th and 50th day respectively. The one patient who survived, recovered

only after a prolonged and exhausting illness lasting approximately 2 months.

Because of the well-known affinity of the *S. viridans* for the heart valves, careful attention was paid to the examination of the heart. No murmurs, embolic phenomena or other evidences of endocarditis were noted in any of these cases, nor were valvular lesions present in the bacteremic patient who came to autopsy.

The sputum was thick and mucoid, sometimes mucopurulent. The prune-juice sputum seen commonly in pneumococcal pneumonia was not observed, although in one of the cases the sputum was bloody for a few days. The *S. viridans* was the predominating organism in the sputum of 4 of the patients, though in 3 of them it was associated with pneumococci. Leukocytosis of a moderate degree was present in all the patients during the acute phases of the illness.

Bacteremia occurred in 3 of the patients, of whom 1 recovered. Both of the non-bacteremic patients died. There does not seem to be any evident relationship between the occurrence of bacteremia and the outcome of the disease.

Analysis of the data in Table 1 shows that in all these cases the *S. viridans* was cultured from one or more of the following sources: the blood, the chest fluid or the lung juice. The mere finding of the organism in the sputum even in pure culture is insufficient proof of the diagnosis, though it should stimulate the search for the organism in the blood, pleural fluid and lung juice, particularly in atypical pneumonias.

It is obvious that the usual rapid method of sputum typing by the capsule swelling phenomenon will fail to disclose the *S. viridans*. Sputum culture on blood agar plates is essential for its isolation. Mouse inoculation followed later by plating of the peritoneal exudate of the mouse is also a satisfactory method. The bile solubility test should be performed routinely to differentiate pneumococcus from streptococcus colonies. This was done in each case of this series.

One of the circumstances that should raise suspicion of the possibility that the *S. viridans* is present either as a primary or secondary invader is the failure of the patient to respond to chemotherapy. Sulfapyridine was used in 3 cases, sulfathiazole and sulfamethylthiazole were used in 1 case each with no perceptible influence on the disease.

In one of the cases the organism was tested for us by Dr. W. D. Sutliff for sulfathiazole resistance. It was found to be resistant. This is suggestive and certainly fits in with the clinical lack of response to chemotherapy.

Literature. Bullowa¹ noted 118 cases where the *S. viridans* was recovered from the sputum among 4416 typed cases of pneumonia in adults. In none of these cases was the organism found in the lung juice or the blood. The mortality rate was 13.5%. Bullowa concluded however, that in most of these cases it was difficult to assess the etiologic significance of the organism recovered. The non-hemolytic streptococcus may have been responsible for the disease or may have been an incidental finding in pneumonia due to another organism. In our cases this element of doubt was greatly reduced by the recovery of the organism from the lung juice or the blood or from both sources.

Cecil¹ in 1918 reported an epidemic of streptococcic pneumonia and empyema occurring at Camp Upton. Sixty-four of the cases were attributed to non-hemolytic streptococci. However, in a personal communication to the authors, Cecil pointed out that in these patients the diagnosis was not confirmed by isolation of the organism from the pleural fluid or blood. It should be borne in mind that when this study was made, a pandemic of streptococcic pneumonia complicating influenza swept the country.

The divergence of opinion regarding the pathogenicity of the *S. viridans* is illustrated by Reimann's statement² that this organism is definitely associated with only one disease, subacute bacterial endocarditis. Menton³ in 1932 found the *S. salivarius* in the lungs and blood at autopsy in several cases of fulminating bronchopneumonia in children. Gerhartz⁴ in 1931 described 3 cases of pneumonia due to the enterococcus with insidious onset, migrating pneumonia and resolution by lysis.

Senerchia and Livengood⁵ reported 8 cases of pneumonia which they attributed to the *S. viridans*. Two of their patients died and the remainder had a prolonged and exhausting illness. The clinical course of these cases lends support, in view of our experience, to the belief that they were due to *S. viridans*, although the organism was recovered only from the sputum in 7 of the cases.

Reimann² reported a series of atypical pneumonias, from 2 of which he was able to isolate a virus. The finding of the *S. viridans* in the sputum, pleural fluid and blood of our cases distinguishes them from Reimann's group. Moreover, the cases described by Reimann had diffuse bronchopneumonia with rarely any evidence of consolidation, while our patients showed consolidation both on physical examination and by roentgenogram.

Summary. 1. We have reported 5 cases of atypical pneumonia in which the *S. viridans* appears to have been the etiologic agent, although it was recovered from sources other than the sputum.

2. An analysis of these cases presents the following features: (a) prolonged severe course (with a high mortality rate); (b) associated reaction with erythrocytosis; (c) failure of response to chemotherapy.

3. Atypical pneumonia not responding to chemotherapy may be caused by the *S. viridans*. A careful search for the organism should be instituted from the blood and pleural fluid in cases of this type.

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**PNEUMOCOCCIC PNEUMONIA: THE SELECTION AND CONTROL OF
SERUM AND CHEMOTHERAPY BY SPUTUM EXAMINATION***

BY ARTHUR W. FRISCH, M.D.

ALVIN E. PRICE, M.D.

AND

GORDON B. MYERS, M.D.

DETROIT, MICH.

(From the Departments of Bacteriology and Internal Medicine, Wayne University
College of Medicine and Receiving Hospital)

DURING the past few years we have been utilizing Wright stained smears of rusty sputum from patients with pneumonia as an index of prognosis and as a guide to therapy. The outcome of the pneumonia could be predicted more accurately by the number of pneumococci in the sputum than by any of the usual prognostic criteria such as type, bacteremia, leukocyte count, duration of the disease, age, and the degree of involvement.^{5,9} The fatality rate was uniformly low in patients with less than 30 pneumococci per field and uniformly high in those with sputum counts over 30 irrespective of the above factors. Furthermore, the specific response of individual patients to serum and sulfonamides could be readily followed by the examination of sputum at intervals during the course of the disease. While the end result of both of these forms of therapy is a reduction in the number of organisms in the sputum and lungs, this is accomplished in a different manner by each of the therapeutic agents. Adequate serum in moderately ill patients brings about a prompt agglutination of the pneumococci in the sputum within 6 to 12 hours, which is usually followed by phagocytosis and a gradual reduction in the number of organisms over a period of several days.^{1,2,3} When large numbers of pneumococci are present, serum is inefficient and actual multiplication may occur despite the presence of excess antibody in the blood.^{1,3,7} The sulfonamides, on the other hand, exert a direct bacteriostatic action which is manifested by a reduction in the number of pneumococci within 12 to 36 hours. A striking effect is obtained in the sputum regardless of the number originally present^{3,4,7} except in the rare instances where drug fastness develops.^{3,4,6} The marked superiority of sulfapyridine, sulfathiazole, and sulfadiazine over serum or sulfanilamide may be best demonstrated in the more severely ill patients with sputum counts exceeding 30 per field.⁹

On the basis of the foregoing observations, the microscopic examination of sputum would appear to be a practical method of individualizing therapy in pneumococcic pneumonia. Thus the mild cases could be differentiated from the severe ones by sputum counts and the dosage of serum or drugs controlled by following the effects in the sputum. Preliminary data supporting this premise have already been presented

* Supported by a grant from the Commonwealth Fund to the Michigan Department of Health Laboratories.

in a therapeutic experiment involving 270 cases of pneumococcal pneumonia.³ There were no deaths in 118 patients with sputum counts below 10 for whom supportive or serum therapy was selected; whereas, the fatality rate was 16% in 138 cases with sputum counts above 10 despite modern chemotherapy. The object of the present communication is to present additional data concerning the sputum count as a means of selecting therapy and also to evaluate it as a method of controlling the dosage of both serum and the sulfonamides in individual patients with pneumonia.

Method. Specimens of rusty sputum were obtained on admission to the hospital, and the number of pneumococci per field was determined by the method previously described.^{3,4} The diagnosis of pneumonia was confirmed by roentgenogram in each case. Therapy was then initiated in accordance with the sputum count as outlined in Table 1. Subsequent specimens of sputum were obtained at intervals of 12 hours or less in order to determine whether or not a therapeutic effect had occurred. When the counts decreased, the dosage was reduced as indicated in Table 1. If the number of pneumococci increased beyond the limits of the range in which the patient was originally classified, therapy was modified to conform with that established for the new zone. The schedule in Table 1 was adhered to as strictly as possible except in the cases with original sputum counts exceeding 50 per field. The fatality rate of 2% in this group that we did not dare risk a relapse by discontinuing therapy too soon. The dosage of 0.5 gm. every 4 hours was, therefore, continued for 2 or 2 days after a full drug effect had been observed in the sputum.

TABLE 1.—THE SELECTION AND CONTROL OF THERAPY BY SPUTUM COUNT

Pneumococci per O. L. L.	Duration of disease (days)	Sputum change	Therapy	Dosage
10 or less	Less than 60 More than 60	— + or ++	Supportive	—
10 or less	Less than 60	—	Serum	10 cc. 4 times daily
11 to 20	All	— or +	Serum and drugs	6 cc. 2 times daily, 10 cc. 4 times daily, 10 cc. 2 times daily, 10 cc. 4 times daily
21 to 50	All	— or +	Serum and drugs	10 cc. 4 times daily, 10 cc. 2 times daily, 10 cc. 4 times daily, 10 cc. 2 times daily
51 to 100	All	— or +	Serum and drugs	10 cc. 4 times daily, 10 cc. 2 times daily, 10 cc. 4 times daily, 10 cc. 2 times daily
More than 100	All	— or +	Serum and drugs	10 cc. 4 times daily, 10 cc. 2 times daily, 10 cc. 4 times daily, 10 cc. 2 times daily

* Serums were given in 10 cc. doses, 4 times daily, for 3 or 4 days.

Results in Cases with Initial Sputum Counts of 10 or Less. When the sputum count on admission did not exceed 10 per field, 118 patients entered the cases were classified as mild pneumonia, and the majority of these patients received supportive therapy. In 103 cases in which the sputum count was 10 or less on admission and the patients received no specific therapy, the fatality rate was 1.9%. In 15 cases in which the sputum count was 10 or less on admission and the patients received specific therapy, the fatality rate was 0%.

pneumococci prior to the 4th day of the disease thus indicating the development of an active immunity, and (b) for those who had been ill longer than 4 days on the assumption that immune bodies would appear in time to dispose of the small number of pneumococci present.* On the basis of the foregoing criteria, 108 patients were started on supportive measures only (Table 2). Nine per cent had positive blood cultures, 16% had leukocyte counts under 10,000 during the acute stages, and 18% showed involvement of more than 1 lobe. The prognosis as based on the initial sputum count was erroneous in 3 cases which proved fatal. The number of pneumococci in the sputum increased in 2 of these, but the institution of chemotherapy failed to prevent death. The fatal outcome was due in part to complicating pericarditis in 1 case and to uremia in the other. In the third patient who died, the pneumonia gradually extended from 1 to 4 lobes despite the fact that the sputum count remained below 10 per field throughout his illness. All 3 cases showed relatively few pneumococci in the lungs at necropsy. In 9 additional cases, the pneumococci increased sufficiently to bring the count within the 11 to 20 range and the appropriate chemotherapy was accordingly instituted, following which a prompt fall in sputum count and an uneventful recovery occurred. The prognosis as based upon sputum counts proved correct in 96 of the 108 cases for whom supportive therapy was originally selected since all recovered without specific treatment. Evidence of active immunity as indicated by spontaneous agglutination of the pneumococci in the sputum was obtained in 72% of the patients. The fact that approximately 90% of the patients made the anticipated recovery without specific treatment proves the validity of the criteria originally set forth in the selection of cases.

When the illness was less than 96 hours in duration and the number of pneumococci in the sputum did not exceed an average of 10 per field, serum was given in doses just sufficient to induce agglutination. Serum therapy was accordingly selected for a total of 114 cases fulfilling the above criteria in order to determine whether or not such small doses were adequate for recovery (Table 2). Eighteen per cent of the cases had bacteremia, 7% had leukopenia, and 20% showed consolidation of more than 1 lobe. Subsequent specimens were examined at 6 to 12-hour intervals during the course of the disease and no additional therapy was given as long as clumping was maintained and the count did not rise above 10. Serum in this dosage proved inadequate in 9 cases. In 7 of these, including 1 fatality, the sputum count increased above 10 per field and chemotherapy was given. In 2 of the 9 patients the sputum count remained below 10, but pericarditis developed; one survived following chemotherapy, but the other expired. The remaining 105 of the original 114 cases recovered with serum therapy alone. Agglutination of the pneumococci in the sputum was induced and maintained in 95% of the patients in this group; so few organisms were

* The spontaneous clumping of pneumococci in the sputum is frequently associated with the appearance of agglutinins in the circulating blood (unpublished data).

present in the other 5% that clumps could not be demonstrated.* The average total dose of serum administered to each patient was 35,000 units, an amount usually considered inadequate by the majority of investigators. In fact, as little as 2,000 units produced prompt agglutination in some cases. The average dose for bacteremias was only 15,000 units and a minimum of 10,000 sufficed in several instances. These data show that small doses of serum as controlled by sputum examinations were adequate for the recovery of over 90% of the patients who satisfied the criteria set forth in the selection of cases.

TABLE 2. SUMMARY OF CASES

Case No.	Dose of Serum	Dose of Supportive Therapy	Time of Death	Bacteremia			Defervescence		
				First Exam	Last Exam	Mean No. of Bacteria	First Exam	Last Exam	Mean No. of Days
1-10	Small doses	Supportive	1-10	18	18	18	18	18	18
11-20	Small doses	Supportive	11-20	18	18	18	18	18	18
21-30	Small doses	Supportive	21-30	18	18	18	18	18	18
31-40	Small doses	Supportive	31-40	18	18	18	18	18	18
41-50	Small doses	Supportive	41-50	18	18	18	18	18	18
51-60	Small doses	Supportive	51-60	18	18	18	18	18	18
61-70	Small doses	Supportive	61-70	18	18	18	18	18	18
71-80	Small doses	Supportive	71-80	18	18	18	18	18	18
81-90	Small doses	Supportive	81-90	18	18	18	18	18	18
91-100	Small doses	Supportive	91-100	18	18	18	18	18	18

* Not a true control; 10% of cases.

* Defervescence within 48 hours; 10% of cases.

Total cases: 100 (10% type I, 2% II, 14% III, 14% IV, 12% V, 12% VI, 12% VII, 12% VIII, 12% IX, 12% X).

The results in the above cases treated with serum and supportive measures compare favorably with those obtained in a group of 118 unselected cases with initial sputum counts of 10 or less who received routine chemotherapy (Table 2). This consisted of an initial dose of 4 gm. of sulfapyridine, sulfathiazole, or sulfadiazine, followed by 1 gm. every 4 hours thereafter until an adequate clinical response was observed. The incidence of bacteremia, leukopenia and multiple lobe involvement in the sulfonamide controls corresponded closely to the averages for the other two groups (Table 2), but the fatality rate and number of complications were not significantly reduced. Defervescence occurred within 48 hours after treatment in 52% of the cases receiving supportive therapy, in 64% of those given small doses of serum, and in 70% of those receiving routine doses of sulfonamides (Table 3).

* The agglutination of pneumococci in the sputum following serum therapy has been described previously together with preliminary data on the control of dosage.† We considered that an appropriate response had been obtained when distinct clumps of pneumococci appeared even though all organisms were not agglutinated. As long as clumping was maintained, no additional serum was given. One dose of serum was sufficient in 51 cases; two were necessary in 21; and three or more were required in 4 patients.

TABLE 3.—CLINICAL RESPONSE TO THERAPY

Sputum count	Therapy	Dosage	Total cases	Fatal-ity (%)	Treatment (average)		Hours to deferves-cence (in %)			Complica-tions (%)	Relapses
					Dose (gm.)	Days	48 or less	49 to 96	Over 96		
10 or less	Supportive	...	97	1	52	28	20	4	
	Serum	35,000 U	105	0	64	20	16	4	4
	Sulfonamides	Routine NC*	118	1	27	4 5	70	15	15	3	4
11 to 20	Sulfonamides	Small C	87	5	13	3.5	47	16	37	14	9
	Sulfonamides	Routine NC	67	9	31	5.2	59	18	23	6	1
21 to 35	Sulfonamides	Moderate C	81	2	21	4.0	35	26	39	10	3
36 to 50	Sulfonamides	Large C	34	9	34	4 7	27	15	58	28	1
Over 50	Combined†	Large C	27	56	45	5 8					
	Sulfonamides	Routine NC	19	79	32	6 5	17	10	73	27	
	Sulfonamides	Large C	24	42	52	7 2					

C = Controlled. NC = Not Controlled.

* Therapy not selected by sputum count.

† An average of 410,000 units of serum was given to each patient who survived.

Results in Cases with Sputum Counts Between 11 and 35. If the initial sputum count exceeded 10 per field, chemotherapy was deemed necessary regardless of the immune state or duration of the disease. For cases within the 11 to 20 range, either sulfapyridine, sulfathiazole or sulfadiazine were given in an initial dose of 2 gm. followed by 0.5 gm. every 4 hours to determine whether such small doses were sufficient to reduce the number of pneumococci in the sputum and to bring about a recovery. A total of 102 cases were treated in this manner (Table 2). Thirty-three per cent had bacteremia, 18% had leukopenia, and 42% showed involvement of more than 1 lobe. There were 6 deaths in the series, 2 of which were due to uncomplicated pneumonia. A third patient died in delirium tremens shortly after the administration of the initial dose; another expired with a Type III pneumonia after recovery from the original Type VII infection; a fifth died in uremia; and the last developed meningitis and expired despite large doses of serum and sulfapyridine. The response in the sputum was unsatisfactory in 13 other cases, but each survived after the dosage of sulfonamide had been increased. Nine relapses occurred in the remaining 84 patients because of too rapid removal of drug, but all recovered without modification of the original plan of treatment. These patients, who constituted 82% of the entire group, received an average of only 13 gm. of sulfonamides over a period of 3.5 days (Table 3). Included among the 84 patients who recovered on such small doses were 23 cases with bacteremia, 14 with leukopenia and 32 with involvement of more than 1 lobe.

Sixty-seven additional patients with sputum counts in the 11 to 20 range and a comparable incidence of bacteremia and multiple lobe involvement who were given routine doses of chemotherapy have been

included as controls for the above group (Tables 2 and 3). The survivors received an average total dose of 31 gm. of drug over a period of 5.2 days. In spite of the fact that the initial and subsequent doses were twice as great as in the group where therapy was controlled by sputum findings, the fatality rate and the duration of the disease were not significantly altered. The incidence of complications and relapses, however, was appreciably lower in the group receiving routine chemotherapy. These data show that over 80% of the cases classified as moderately ill on the basis of an initial sputum count between 11 and 20 will recover on half the customary dose of sulfonamides.

When the admission sputum count ranged between 21 and 35, chemotherapy was given in an initial dose of 1 gm. followed by 1 gm. every 4 hours. As soon as the count fell below 10 per field the dosage was reduced by half and the drug was discontinued when a full effect was observed (Table 1). As a consequence of the control of dosage by sputum examination the average total drug given to the 81 patients treated in this manner was 21 gm. over a period of 4 days. Although the disease was somewhat more severe than in the above group given routine chemotherapy as shown by the higher sputum count and the greater incidence of multiple lobe involvement and leukopenia, the fatality nevertheless was very low, amounting to only 2% (Table 2).^{*} The clinical response, however, was slower, defervescence occurring within 48 hours in only 35% of the 79 cases which recovered in contrast to 59% among those treated routinely (Table 3). These data show that both the sulfonamide dosage and the duration of therapy may be safely controlled by sputum examination and that excellent end results may be obtained with less than the customary amount of chemotherapy.

Results in Cases with Sputum Counts Over 35. Those patients with sputum counts between 36 and 50 per field were classed as severely ill and were, therefore, considered as candidates for the sodium salts of the sulfonamides in double the routine dosage. They received 4 gm. intravenously on admission followed by 4 gm. within the next 4 hours and 2 gm. orally every 4 hours thereafter until an effect was observed in the sputum. The characterization of the pneumonic process as severe was also borne out by the fact that 68% had bacteremia, 41% showed leukopenia, and 76% had 2 or more lobes involved.[†] The fatality rate of only 9% in the presence of such a high incidence of unfavorable prognostic factors may be ascribed to the intensive chemotherapy, as will be more clearly shown in the group with sputum counts exceeding 50. The average total dosage of sulfonamide was 34 gm., approximately half of which was administered during the first 24 hours, the remainder given in diminishing doses during the next 3.7 days. Defervescence occurred within 48 hours in only 27% of the cases. The longer course was in part attributable to the fact that 28% had complications (Table 3).

The last group of patients with sputum counts over 50 per field were classed as overwhelmed pneumonias and, therefore, received

* A decrease in the number of pneumococci in the sputum occurred in 94% of the cases

† A therapeutic response was observed in the sputums of 92% of the cases

intensive therapy (Table 2). Early in the study it was felt that large doses of serum coupled with intravenous sulfonamides offered the greatest hope for recovery in this group of cases. The fatality rate, however, among 27 patients treated in this manner was 56%. The survivors received an average dose of 410,000 units of serum plus 45 gm. of drug over a period of 5.8 days.* Inasmuch as cases of this severity offered an excellent means of determining whether supplementary serum contributed significantly towards the recovery, we accordingly treated a group of 43 comparable cases with sulfonamides exclusively, with the resultant fatality of 58%. Among this group of 43 patients there were 19 who received the routine dosage of 4 gm. of sulfonamide on admission and 1 gm. every 4 hours thereafter. In those who recovered, the average total dose was 32 gm. over a period of 6.5 days. These cases were contrasted with a group of 24 others in which the sodium salt was administered intravenously in large doses as described above. Those that recovered received an average total of 52 gm. of drug over a period of 7.2 days without serious toxic reactions. The fatality in the latter group was 42% in contrast to 79% in the former given routine doses (Tables 2 and 3).† These data support our contention that the overwhelmed cases may be detected by means of the sputum count. Furthermore, they show that supplementary serum contributes insignificantly towards recovery; that massive doses of sulfonamide intravenously offer a greater chance of survival; and finally (Table 3), a clinical response within 48 hours is the exception rather than the rule in such severely ill patients.

Discussion. The determination of the average number of pneumococci in Wright stained smears of rusty sputum has proved to be a simple and reliable method for the selection of therapy in pneumococcic pneumonia. The admission sputum count was of considerable aid in differentiating the mild and moderately ill from the critically ill patients. Although it was shown that over 90% of the mild cases recovered with minimal doses of serum or with supportive treatment only, we believe that these patients would have responded more promptly to small amounts of sulfapyridine, sulfathiazole or sulfadiazine and with less danger of extension or relapse. The chief value of the admission sputum count lies in the fact that it provides a means for the prompt recognition of critically ill patients who should have immediate and intensive therapy. Our original premise that large doses of serum in conjunction with the sulfonamides would offer more chance of recovery than chemotherapy alone was not borne out by the results. Although the effects of both agents were demonstrable in the sputum, and although the eventual reduction in the number of pneumococci was accomplished by two entirely different mechanisms, the data showed that the beneficial results with combined treatment were primarily due to the sulfonamides and not to the serum.‡ In addition.

* An effect from serum was observed in 45% and from chemotherapy in 52% of the cases.

† An effect from therapy was noted in the sputums of 68% and 47% respectively.

‡ Early in the study 8 cases with sputum counts exceeding 50 were treated with serum alone and all expired.

the clearly demonstrated superiority of intravenous chemotherapy in large doses over oral drug in routine doses again emphasizes the importance of adequate treatment in the critically ill patients with sputum counts exceeding 50. Since a high fatality rate still prevails in this group and because no serious toxic manifestations resulted from the doses used, the desirability of even larger doses during the first 48 hours should be seriously considered. In our opinion the major problems are first, to keep the patients alive long enough for the sulfonamides to exert an effect, and second, to carry them through the complications that so frequently develop. Thus, among the fulminating cases with high sputum counts a total of 25 of the 40 deaths occurred within the first 24 hours after therapy had been started. Ten of the 15 which survived more than 24 hours showed a maximal reduction in the number of pneumococci in the sputum and in the lungs at necropsy. Purulent complications were responsible for 6 of the 10 deaths and serious associated diseases were important contributing factors in the other 4 cases. The remaining 5 deaths included 4 cases in which the pneumococci had become resistant to the sulfonamides and 1 patient who expired within 36 hours after therapy had been instituted. In view of the fact that intravenous chemotherapy in the doses used reduced the fatality rate from 79 to 42%, it is possible even larger doses might be more effective when the sputum count exceeds 50 per field.

Supplementary serum has been generally advocated for patients who fail to respond to drugs within the first 48 hours after therapy has been instituted. Our data are at variance with this concept since it has been shown that even under optimal conditions for recovery (sputum counts below 10) defervescence occurred within 48 hours in only 70% of the cases treated with sulfonamides. Furthermore, the clinical response was markedly delayed in the overwhelmed cases, where it was found that less than 20% showed a defervescence within 48 hours after treatment with massive doses of sulfonamides often supplemented by serum. As a general rule, a full bacteriostatic effect from chemotherapy was demonstrable in the sputum and lungs⁷ of the vast majority of patients who lived more than 48 hours after treatment had been instituted. A failure to obtain a clinical response after 48 hours of chemotherapy was attributable either to the overwhelming nature of the primary disease, to complications, occasionally to drug resistance, or to other factors which are not at present understood. Relatively few cases were seen in which the pneumococci were refractory to the bacteriostatic action of the sulfonamides. Among the total 694 cases studied there were only 12 (2%) who were classified as resistant either because the drug failed to reduce the number of pneumococci or because the organisms, after an initial decrease, returned to the sputum while the drug was being administered.^{3,4,6} As a result of these observations we believe that the use of serum should be limited to the few cases in which drug resistance is demonstrable.

The reliability of the sputum as a method for the control of serum dosage is evident from the data presented. During the period when

serum was the only available specific remedy for pneumonia, the standard dosage was based largely on clinical experience. In an attempt to prevent failures in the seriously ill patients, there was a trend toward a gradual increase in the recommended dose of serum. The utilization of the sputum as a means of controlling serum dosage has shown that in more than 90% of properly selected cases, an average of 35,000 units was sufficient to effect a recovery. The Francis test as a method of judging serum dosage has been disappointing in our hands. Over 60% of the cases gave false positive skin reactions on admission despite the fact that polysaccharide from 4 different sources was tried. We also noted that the skin test remained negative in many patients who responded well to minimal doses of serum. When excessive doses were used, a positive test was elicited.

The moderate to mildly ill patients with sputum counts under 35 who constituted 85% of the total admissions have hitherto received larger amounts of sulfonamide over a longer period of time than is actually necessary. By reducing the dosage as the number of pneumococci decreased and by withdrawing the drug after a full effect was evident in the sputum, satisfactory results were obtained with a total dose of 10 to 25 gm. administered over a period of 3.5 to 4.5 days. In these cases it was found that minimal effective blood concentrations were between 3 and 4 mg. per 100 cc. for sulfapyridine and sulfadiazine and between 1 and 2 mg. per 100 cc. for sulfathiazole. Although the initial small dosage did not appear to encourage the development of drug resistance, the incidence of relapses and complications was higher than in a comparable group of cases receiving routine doses (Table 3). For the above reasons we believe that the small dosage scheme should be so modified that larger amounts of drug are given during the first 24 to 48 hours and the subsequent dosage controlled according to the sputum response. By this method the maximum therapeutic efficiency of the sulfonamide drugs would be insured, but their toxic and sensitizing effects¹⁰ would be minimized.

Summary. The treatment of pneumococcic pneumonia was individualized by dividing the cases into 3 major prognosis groups according to the number of pneumococci in Wright stained smears of rusty sputum. The cases in the first group represented approximately 50% of the total admissions and were classed as relatively mild on the basis of sputum counts of 10 or less during the course of the disease. Over 95% of these recovered with supportive therapy, with small doses of serum or with sulfonamides. Although the very low fatality rate of 2% was not appreciably altered by sulfonamides, the pneumococci were more effectively prevented from multiplying and a more rapid defervescence was induced. The patients in the second group represented approximately 35% of the total admissions and were classed as moderately ill on the basis of sputum counts between 11 and 35 per field. By decreasing the dosage when a therapeutic response was elicited in the sputum, the total amount of sulfonamide administered was significantly reduced without affecting the final fatality rate. The last group with sputum counts over 35 included only 15% of the total

cases, but was responsible for 70% of the deaths. The sodium salts of the sulfonamides in large doses intravenously were the most effective therapeutic agents. Supplementary serum proved to be of no additional value in the most severe cases with sputum counts exceeding 50 per field. From this study it was concluded that the initial and subsequent examination of sputum can be effectively utilized as a method for the selection and control of therapy in pneumococcal pneumonia.

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XANTHOMATOSIS—HAND-SCHÜLLER-CHRISTIAN TYPE: REPORT OF A CASE WITH PULMONARY FIBROSIS

BY JAMES H. CURRENS, M.D.

FELLOW IN MEDICINE, MAYO FOUNDATION

AND

WALTER C. POPP, M.D.

SECTION ON THERAPEUTIC RADIOLOGY, MAYO CLINIC
ROCHESTER, MINN.

This disease was first described by Schüller* in 1915 and elaborated upon by Christian in 1919 and Rowland in 1928. It has since been accepted as a distinct clinical entity, as is evidenced by the frequent reports of cases of it in the literature. The presence of (1) map-like defects of the skull, (2) exophthalmos, and (3) signs of hypopituitarism (diabetes insipidus and dwarfism) have been generally accepted as the triad necessary to the making of a conclusive diagnosis. Experience, however, has shown that such actually is not the case, since only one or two of the clinical signs may be present. It has been found also that involvement may occur in any part of the reticulo-endothelial system in the body. Such clinical signs as lymphadenopathy, pulmonary fibrosis, hyperpyrexia, hepatomegaly and splenomegaly, involvement of the long bones and icterus may be found.

The etiology of the disease remains obscure, although it is thought to be due probably to a disturbance in lipid metabolism, especially of cholesterol metabolism, and of the cholesterol esters, possibly in the cells of the reticulo-endothelial system. Thannhauser, in his recent (1940) complete monograph referred to this disease as a primary essential xanthomatosis of the normal cholesteremic type. However, the histologic appearance of some of the tumor suggests very strongly to some pathologists that the disease may be an infectious type of granuloma.

* The first clinical description of this condition was made by Alfred Hand (Pr. Phila. Path. Soc., 1895), who recognized the main triad but, like the other early investigators, has incorrect ideas as to its etiology. EDITOR.

The following case is presented as one of xanthomatosis (Hand-Schüller-Christian's type) with the usual osseous lesions and also extensive pulmonary fibrosis. Several interesting features are presented, including the results of Roentgen therapy.



FIG. 1.—a, Parietal bone lesions before Roentgen therapy; b, lesion in the neck of the left femur before Roentgen therapy.

Report of a Case. The patient, a 29 year old single woman, entered the Mayo Clinic on January 5, 1942. At the age of 7 years she had had poliomyelitis which resulted in partial paralysis of the right arm and left leg and moderate scoliosis of the thoracic part of the spinal column. In July, 1938, pain and stiffness developed in the left hip, persisted for 2 weeks, and then subsided. Similar symptoms returned 6 months later and were present for 2 weeks. In March, 1941, she noted intermittent twinges of pain over the right parietal portion of the skull, followed in 6 months by a palpable swelling in this region. This swelling persisted and seemed to have become somewhat larger since it had been first noted. In November, 1941, a dull aching pain developed in the left hip, associated with soreness on motion. This pain became worse and prompted the patient's visit to the clinic.

Physical examination revealed a thin woman with moderate dorsal kyphosis and moderate atrophy of the muscles of the right arm and left leg. Over the right midparietal region of the skull was a soft, raised zone with discrete borders about 6 cm. in diameter which was tender on palpation. Results of thoracic examination were negative. The heart rhythm was regular, sounds were normal, and the rate was 110. The blood pressure was 120, systolic, and 85, diastolic, expressed in millimeters of mercury. The right kidney was palpable. Over the greater trochanteric region of the left thigh there was tenderness to palpation, and motion of the left hip was mildly limited because of pain. The patient weighed 95 pounds (about 43 kg.).



FIG. 2.—Pulmonary lesion before Roentgen therapy.

Examination of the blood revealed a value for hemoglobin of 11 gm. per 100 cc. and an erythrocyte count of 4,810,000. The leukocyte count was 8600, with a differential count of 23% lymphocytes, 12% monocytes, 62% neutrophils, 2% eosinophils and 1% basophils. Examination of blood smear demonstrated mild hypochromic anemia. Results of serologic examination for syphilis were negative. Roentgenograms of the skull disclosed an irregular zone of destruction of bone in the right parietal region (Fig. 1a). In the neck of the left femur was a similar defect (Fig. 1b). A roentgenogram of the thorax disclosed bilateral extensive fibrosis (Fig. 2). Results of roentgenograms of the rest of the long bones and hands were negative. Results of blood lipid studies were as follows: cholesterol 177, cholesterol esters 120, fatty acids 327, and total lipoids 501 mg. per 100 cc. of plasma. The value for blood calcium was 10.2 mg., for phosphorus, 3.9 mg., and for phosphatase 1.6 units, per 100 cc. of serum. The value for plasma proteins was 7.9 gm. per 100 cc., with a ratio

of 1.4:1. The sedimentation rate was 44 mm. per hour. The reaction to the Mantoux test was negative in the second-strength solution. The basal metabolic rate was +15. On January 10, 1942, the extradural swelling on the right side of the skull was removed and the pathologic report was: "Hand-Schuller Christian's disease with areas of necrosis and hemorrhage." Chemical



Fig. 3.—*a*, Parietal lesion after Roentgen therapy; *b*, lesion in the neck of the left femur after Roentgen therapy.

analysis of this tissue for the lipoids revealed the following: cholesterol 0.69%, cholesterol esters 0.29%, lecithin 0.42%, fatty acids 1.36%, and a total lipid of 2.05% of the wet weight of the tissue.

The cystic-like zones involving the calvarium and femur were the outstanding features of the case, and accounted for the symptoms of the patient. However, the finding of what appeared to be diffuse fibrosis of the lungs was

unusual. The relatively low amount of fat found in analysis of the tissue taken from the skull reveals that the granulomatous process at this stage is not rich in cholesterol and suggests that the process was relatively old. The pulmonary fibrosis likewise suggests that the disease was fairly long standing. However, in one case in which the patient was a child, recently observed by Hampton, the roentgenologic picture of the lungs changed from that of a miliary process not unlike miliary tuberculosis to that of extreme pulmonary fibrosis and emphysema, within the course of 3 months. At necropsy the alveolar walls were found to be destroyed and the interstitial tissue of the lungs was heavily infiltrated with granulomatous tissue. On the basis of Hampton's observations it seems likely that what appears to be fibrous tissue in the roentgenogram



FIG. 1 —Pulmonary lesion after Roentgen therapy.

actually may be granulomatous tissue, although the ultimate result probably is fibrosis.

Roentgen therapy was begun on January 17. One treatment to the zone of involvement in the right portion of the calvarium and one anterior and one posterior field to the head of the left femur, were employed. The treatments were administered with a moderate voltage technique (130 kv. constant potential), and a total dose of approximately 270 r was utilized. Because of the possibility that the lesions in the lungs may have had a granulomatous basis, one area of treatment was given to the left lung both anteriorly and posteriorly. The treatment to the lung was carried out in this manner so that a comparison might be made between the treated and untreated side of the lung. Two addi-

tional courses of treatment were administered at monthly intervals. The last examination was done on June 17, and marked improvement was found in the osseous lesions (Fig. 3a and b). The last roentgenograms of the thorax disclosed some slight evidences of improvement (Fig. 4).

Comment. This case is unusual in that it presents pulmonary fibrosis which in the past has been seen rarely in connection with xanthomatosis. The improvement in the osseous lesions is typical of the changes seen in juvenile xanthomatosis after Roentgen therapy. In our experience Roentgen therapy in moderate doses causes a definite therapeutic response, whereas large doses call forth little or no response.

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THE ANTIBACTERIAL ACTION OF THE LACTIC ACID AND VOLATILE FATTY ACIDS OF SWEAT*

BY OLAF BERGEIM, PH.D.

AND

THEODORE CORNBLEET, M.D.

CHICAGO, ILLINOIS

(From the Departments of Physiological Chemistry and Dermatology, University of Illinois College of Medicine)

PECK, Rosenfeld, Leifer and Bierman³ have shown that thermal sweat may have fungistic and fungicidal properties at a pH below 7, particularly when concentrated, and that these properties depended on its content of acetic, propionic, caproic, caprylic, lactic and ascorbic acids. They also found topical applications of these acid ingredients of sweat to be valuable in the treatment of fungous infections.

One of us has been interested in the rôle of the volatile fatty acids in the inhibition, under certain circumstances, of the growth of microorganisms in the intestines of animals and man. In order to interpret these results it was necessary to study the relation of pH and of acid concentrations of the volatile fatty acids to their antibacterial action.^{1a,b} These results are also applicable to sweat and should help to clarify the significance of the volatile fatty acids in this secretion, as do also certain other analogies between the situations existing in perspiration and in the intestinal contents. Some observations on sweat made from this viewpoint are here reported.

Methods. Sweat specimens were collected as follows: The subjects were encased in a rubber bag as far as their necks and seated in a heat

* The expenses of this investigation were met in part by grants made to the University of Illinois by Standard Brands, Inc.

cabinet. Incandescent lamps furnished sufficient heat to obtain from 100 to 200 cc. sweat in 20 to 30 minutes. In some cases, specimens were collected after the individual had been thoroughly scrubbed to remove any evaporated sweat from the skin surface. Other specimens were obtained without scrubbing so as to include such dried sweat. Serial specimens were also collected in order to see if there were any changes in composition during the sweating period.

Total volatile fatty acids were determined by acidification with sulphuric acid and distillation with additions of water until all volatile acid had been driven over, followed by titration, using phenolphthalein as an indicator, after the distillates had first been aerated for 15 minutes with a current of air free from carbon dioxide. Observations as to the nature of the volatile acids present were made using the method of Werkman.⁴ Lactic acid was determined by the method of Friedemann and Graesser.⁵ Ammonia was determined colorimetrically using Nessler's reagent. pH determinations were made with the glass electrode.

Lactic Acid in Sweat. The antibacterial action of the acids in sweat may depend in part upon their production of an inhibitory pH. For such inhibition, however, most microorganisms require a pH of below 5. In samples of heat sweat we have noted pH values as low as 5.1 but the average was 5.7. From our published studies such pH values cannot be expected to be very effective in sterilization. Effectiveness depends, however, also upon the nature of the acid. The acid present in sweat in largest amounts is lactic acid (about 0.1% or about 0.01 N). Aside from the pH effect, the undissociated lactic acid also has some influence. Our observations on lactic acid indicate, however, that its molecules have a low sterilizing value (lower than that of acetic acid or any of the other volatile fatty acids) and are so few in number at the average pH of heat sweat that the lactic acid of such heat sweat could hardly have more than a mild antibacterial action with regard to most organisms. Thus lactic acid in 0.1 N solution had no inhibiting effect on the growth of *Esch. coli* when adjusted to pH 6, although at pH 5 it had some action. Of course some organisms are more susceptible than *Esch. coli* as shown in a previous paper.^{1a,b} Concentration of perspiration by evaporation on the surface of the skin may, however, obviously alter the situation. Evaporation to one-tenth volume or less might bring the lactic acid normality above 0.1 and if the pH falls at the same time or remains constant at near 5 fairly effective conditions might be expected. Since lactic acid because of its larger quantity must preponderate in its effect on the pH of the sweat and because the volatile fatty acids appear to be largely formed from the lactic acid, this acid must be of primary importance.

Lactic acid appears to be secreted as such by the skin since it is present in the sweat of subjects who have been thoroughly scrubbed and since it usually decreases rather than increases in amount on incubation of sweat (Table 3). The secretion of lactic acid seems therefore to be the more fundamental process in the acid bath of the skin and determinations of lactic acid in sweat may therefore be of interest. The

necessity for a suitable pH (5.5 or lower) for its action on organisms must however never be disregarded since neutral lactates, such as sodium lactate have little if any effect.

pH of Sweat. We have found the pH of heat sweat to vary from 5.1 to 6.95 in 24 cases studied with an average pH of 5.7. The pH of the more acid of these sweats may be sufficient together with the molecular effects of lactic and fatty acids present to have some, but hardly any strong, antibacterial action. Any influence might be expected on the growth of only the more susceptible microorganisms. Ordinarily, of course, sweat is concentrated upon the surface of the skin by evaporation and since lactic acid is not volatile, a fall in pH with consequent increase in antiseptic powers might be expected. We have evaporated heat sweats at 40° C. in a current of air and found significant decreases in pH. Thus 4 sweats having pH values of 5.2, 5.3, 5.6 and 6.0 on concentrating 23 to 50 times gave values of pH 5.0 to 5.1. These changes in pH are not great, yet taken with the increase in lactic acid concentration to 0.2 N or higher may be of importance, as the growth of *Esch. coli* for example is inhibited at pH 5 by about 0.1 N lactic acid and other organisms are still more susceptible.

The influence of evaporation of sweat on the pH is not, however, a simple one since bacterial action on sweat constituents occurs simultaneously with such evaporation. Apparently the skin bacteria convert some of the lactic acid to volatile fatty acids. This might have little effect on pH. The action of organisms on organic nitrogen compounds of sweat, particularly urea, results in ammonia formation. This ammonia has a neutralizing effect on the acids. Twenty samples of heat sweat showing pH values from 5.1 to 6.5 were incubated at 37° C. for 18 hours. The resultant pH values varied from 6.25 to 8.30 and were mostly above pH 7.0. Some of the results are included in Table 2. In alkaline or neutral solution lactic acid and the volatile fatty acids are very ineffective. If it were not for evaporation, therefore, sweat would rapidly lose the mild antiseptic action it might originally have had. On incubation of sweat, ammonia nitrogen may rise from 5 mg. or less per 100 cc. to 25 mg. or more. This amount of ammonia is sufficient to account for the neutralization of lactic and other acids that occurs in the incubation.

On evaporation of incubated sweat the pH gradually falls. Thus a specimen of sweat with a pH of 6.1 on incubation for 18 hours had a pH of 7.0, and on concentration at 40° C. in a current of air came back to 5.9. Other cases where concentration and incubation went on together over a period of about 6 to 8 hours gave final pH values of near 5.0. Such tests may more nearly approximate conditions occurring on the skin.

The change from alkaline to acid solution on evaporation is apparently due to the fact that lactic acid is non-volatile and the so-called volatile fatty acids are also less volatile than ammonia, so that ammonia passes off leaving most of the acids behind. Thus a specimen of sweat having an ammonia concentration of 6 mg. per 100 cc. was incubated at 40° C. for 18 hours and ammonia went up to 24 mg. per 100 cc. The

incubated sweat was concentrated 50 times by evaporation at 40° C. and ammonia fell to 8 mg. The instability of the ammonium salts of the acids involved is well recognized.

That the pH of sweat is not due to any great extent to the presence of carbon dioxide is indicated by the fact that when air free from carbon dioxide was bubbled for 15 minutes through samples of sweat kept at 60° C. there was a change of only about 0.1 in the pH of the sweat (as from 6.1 to 6.2).

The Volatile Fatty Acids. Determination of the total volatile fatty acid of sweat is a relatively simple procedure. Characterizing the individual fatty acids present is difficult, especially with the small amounts present in sweat. Peck *et al.*³ give figures for percent of various acids as acetic 0.0096, propionic acid 0.0062, caprylic and/or caproic acid 0.0016. Since methods of analysis are not given it is not clear whether formic and butyric acids were found absent or are included in the above fractions. Using the method of Werkman⁴ we obtain figures corresponding to 75 to 90% acetic acid and 10 to 25% of propionic or butyric acids. More work on this point is needed but since acetic acid appears ordinarily to definitely predominate, and the antibacterial actions of butyric and propionic acids appear not to be greatly different, no large error of interpretation is likely to be involved in this uncertainty, nor even by the assumption that the total volatile acids will be just slightly more effective than an equivalent amount of acetic acid.

To determine whether the volatile acids were original constituents of the sweat secretion or were formed on the surface of the skin two types of experiments were made. In one series the heat sweat was collected in 2 or 3 successive portions of 100 cc. or more each. The first sweat together with the previous scouring should have washed off most of the adherent perspiration so that later samples should be a purer secretion. The pH values and total volatile acids of first and final sweat samples in 5 cases are given in Table 1.

TABLE 1.—THE PH VALUES AND TOTAL VOLATILE ACIDS OF FIRST AND FINAL SWEAT SAMPLES.

Subject	First sweat specimen		Final sweat specimen	
	pH	Volatile acids (normality)	pH	Volatile acids (normality)
1	5.45	0.004	6.15	0.002
2	5.38	0.009	6.10	0.004
3	5.60	0.002	6.00	0.002
4	5.30	0.001	6.10	0.001
5	5.10	0.001	5.60	0.0007

It will be noted that volatile fatty acids decreased on repeated sweating except where the value was already low. In many other cases also, where but one specimen of sweat was obtained the total volatile acids were in the neighborhood of 0.001 N, a very low value. The lowest value obtained was 0.0007 N. It is not excluded that still lower values might be obtained by still better preliminary cleansing of the skin and decreasing to a minimum the degree of bacterial action permitted during collection of the specimen. It is therefore doubtful

whether any appreciable amounts of volatile acids are actually secreted in sweat. This is in line with the finding of practically no volatile acids in urine, where lactic acid is however found. Apparently the volatile acids formed in metabolism are very rapidly oxidized in the body so that they do not accumulate in the blood or appear in the urine.

If the volatile fatty acids are not excreted in sweat or only in small amounts they must be formed on the skin by bacterial action. Experiments on the incubation of sweat support this view. Sweat was incubated at 37° C. for 18 hours. Some results follow:

TABLE 2.—CHANGES IN SWEAT ON INCUBATION

Subject	pH		Volatile acids (normality)	
	Before	After	Before	After
1	6 95	8 00	0 0037	0 0100
2	6 46	7 00	0 0010	0 0035
3	5 75	7 17	0 0022	0 0084
4	6 15	7 46	0 0020	0 0060
5	5 38	8 05	0 0090	0 0125
6	6 10	8 30	0 0043	0 0105
7	6 10	7 00	0 0010	0 0025
8	5 30	5 90	0 0010	0 0028

It is evident that the volatile fatty acids of sweat may increase markedly on incubation and it appears that most if not all of the volatile acids found in sweat that has remained for some time on the surface of the body must be due to bacterial action.

That the volatile fatty acids are largely formed by bacterial action on the lactic acid of the sweat is indicated by the fact that on incubation of sweat the fatty acids rise and the lactic acid decreases to about the same extent (Table 3). A similar formation of fatty acids from lactic acid occurs in the intestines. While it is not certain that all of the fatty acids are formed from lactic acid, it is not clear from our knowledge of the chemistry of sweat just what other constituent might yield fatty acid. No study has been made of the bacteria concerned. Incubation of sweat made sterile by Berkefeld filtration causes no decrease in lactic acid or increase in volatile acids.

TABLE 3.—EFFECT OF INCUBATION OF SWEAT ON LACTIC ACID AND ON VOLATILE FATTY ACIDS

(Incubation for 24 hours at 37° C. Results expressed in normality)

No.	Sweet lactic acid		Volatile fatty acid		Lactic acid decrease	Volatile acid increase
	Before incubation	After incubation	Before incubation	After incubation		
1	0 018	0 015	0 001	0 003	0 003	0 002
2	0 025	0 018	0 002	0 006	0 007	0 004
3	0 028	0 022	0 002	0 005	0 006	0 005
4	0 018	0 017	0 001	0 002	0 001	0 001

The volatile acids do not therefore appear to be primary constituents of sweat and amounts present are naturally variable. That nevertheless the volatile acids may be significantly antibacterial upon the skin has been indicated by the work of Peck *et al.* Our work on the fatty acids indicates in some detail what conditions must exist with regard to them if they are to be effective. It is doubtful whether they ever

have much influence simply through their effect upon the pH of the sweat since they are commonly present in definitely smaller amounts than lactic acid and are weaker acids. Their influence must be due chiefly to undissociated molecules of the acids and will depend upon the nature of the acid and upon its dissociation which in turn depends upon the dissociation constant of the acid and upon the pH. Thus acetic acid has an ionization constant of 1.85×10^{-5} . If we start with 0.1 N acetic acid (pH 2.89) and add NaOH to obtain a hydrogen-ion concentration of 1.85×10^{-5} , (pH about 4.7) there will be an equal number (0.05 N) of acetic acid molecules and of acetate ions. Neutralizing to pH 5.7 the acetic acid molecules would be about $\frac{1}{3}$ th as great (0.09 N) and at pH 6.7 about $\frac{1}{10}$ th as great. Acetic acid is thus very effective at pH 5, fairly effective at pH 6, but becomes rapidly ineffective above that point. Lactic acid having an ionization constant of 1.4×10^{-4} would be half in the molecular form and hence have a high molecular effect at pH 3.85. It would have a fair effect at pH 4.85, but a low effectiveness at pH 5.85 or higher. There is thus a range of about pH 5.4 to 6.2 where lactic acid tends to be ineffective but acetic acid (also propionic and butyric acids) may still exert an appreciable influence on bacterial growth.

Where the lactic acid of the sweat succeeds in maintaining a pH of 5 or lower its effect may predominate, but when it falls to around pH 6 from any cause the volatile acids may be more important. The volatile acids thus form a sort of "second line of defense." This is essentially the same thing that occurs in the intestines where lactic acid production from carbohydrate may inhibit some bacterial growth, but as this acid is absorbed or neutralized to a pH in the neighborhood of 6, the production of volatile acids from the lactic acid extends the protection to these higher pH levels. As in the intestines the situation is quite complicated, making difficult an exact evaluation of the importance of the volatile acids in a given case. We have variations in amount of sweat secreted, in the composition of this sweat on different areas of the skin, in the degree and rapidity of evaporation, and in the character of the skin flora. Pathologically also the resistance of the organisms concerned in the skin pathology must be involved as well as any influence of pathology on perspiration. We have published results on the resistance of a variety of organisms to the volatile acids.^{1a,b} Peek *et al.* have published results with certain fungi.

Of the 18 organisms studied by us, many were inhibited by 0.005 N volatile fatty acid at pH 5.4 to 5 or lower and most of them by 0.01 N volatile fatty acid at pH 5 or lower. Seven organisms were inhibited by 0.025 N butyrate at pH 6.4, and 11 at pH 6.0. A sweat containing 0.025 N volatile fatty acid and hence effective against many organisms in the neighborhood of pH 6 could readily be formed by evaporation of fresh or incubated sweats to from $\frac{1}{3}$ th to $\frac{1}{10}$ th their volumes and where such conditions are found upon the skin a protective action may be postulated. At reactions above pH 6.5 such protection must be very slight no matter what amount of lactic or volatile acids may be present.

Peck *et al.* have reported some success in the use of volatile acids in the therapy of certain skin disorders. We believe our reports have added something to the rationale of such use by emphasizing the limits of pH at which effectiveness of the various acids may be expected and by pointing out that buffer solutions of these acids should be much preferable to use than the pure acids because their buffering effect helps to maintain the given acidity and because the irritant effect of low pH in itself is much decreased. Thus solutions of the volatile fatty acids, especially acetic and propionic from 0.01 to 1 N neutralized to from pH 4.5 to 6.0 should be given further trial. As antiseptics such solutions have the advantage of low toxicity.

Studies on the pH, lactic and other acid concentrations on various skin areas, with special reference to certain types of skin disorders, are being carried out as well as studies of the conditions under which applications of buffer solutions of the acids may be useful.

Summary. An effort has been made by the application of previous findings from this laboratory on the factors governing the antibacterial action of the volatile fatty acids to clarify the relation of these substances to the antiseptic action of sweat. While interpretation is complicated by the variety of factors involved, the general picture seems to be as follows: Freshly secreted sweat may have a mild antiseptic action due largely to its acid pH, for which lactic acid is largely responsible. Evaporation of such sweat on the surface of the skin or elsewhere tends to lower the pH and increase the lactic acid concentration, so that the sweat becomes much more effective in this regard. Tests on incubation of sweat show, however, that there is also a tendency for the sweat to become alkalinized, due to ammonia formation by bacteria from the urea present. Ammonia is more volatile than lactic acid, however, so that on evaporation much of this ammonia is lost and the lactic acidity regained. The volatile fatty acids are largely if not entirely formed on the surface of the skin by bacterial action upon the lactic acid. Above pH 5.3, lactic acid is so completely ionized that few undissociated molecules of acid (on which much of the antibacterial action of the acid must depend) are present. The chief protective value of this acid lies therefore below pH 5.3. The volatile acids are less dissociated (and hence more effective) in the pH range of 5.3 to 6.2. Their most important rôle would appear therefore to be the extension of some degree of acid protection into these higher pH levels which also exist on the skin under certain conditions.

Conclusions. Sweat as secreted contains lactic acid in amounts sufficient to give it some bactericidal action. Evaporation on the skin increases the lactic acid concentration and renders the sweat much more effective. The concentration must be such as to give a pH of 5.3 or lower for the lactic acid to have much effect. The volatile fatty acids of sweat appear to be formed by bacterial action on the lactic acid. They are present in smaller amounts than lactic acid in sweat but are relatively more effective in the range of pH 5.3 to 6.2. They may therefore extend the antiseptic action of the sweat into the regions of the skin where this pH range prevails and thus act as an additional

safeguard against skin infections. This can be of some importance in such regions as the axillae which are relatively less acid. Chemical changes occurring in sweat after secretion are discussed.

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THE PRESENT POSITION OF GASTROSCOPY IN THE DIAGNOSIS OF GASTRIC DISEASE*

By MOSES PAULSON, B.S., M.D., F.A.C.P.

ASSOCIATE IN MEDICINE, ASSISTANT VISITING PHYSICIAN AND CONSULTANT IN DIGESTIVE DISEASES, DIAGNOSTIC CLINIC, THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL
BALTIMORE, MD.

(From the Gastro-intestinal Nutritional Clinic and Laboratories of the Department of Medicine)

My teaching and consultation experiences indicate that many clinicians are still unaware of the position of gastroscopy in the diagnosis of gastric disease despite an increasing literature on the subject. This may be due in part to the recentness of the revival of gastroscopy and in part to the fact that many of the publications are written for specialists in the field. This article is written to point out simply and clearly when gastroscopy might be employed and when not, and what might be expected from it.

Gastroscopy is the direct visualization of the surface of the stomach by means of an illuminated instrument. It is almost the oldest of endoscopic methods, but the most recent to tend toward perfection through the development in 1932 by Georg Wolf and Rudolf Schindler¹ of a flexible gastroscope. Gastroscopy began in 1868 when Kussmaul first attempted it by means of a straight tube; Mikulicz in 1881, Rosenheim in 1895, and Elsner in 1911 were pioneers. All attempts were unsatisfactory due to technical difficulties: these consisted chiefly in the inability to construct a satisfactory optical system; in accidents, particularly to the esophagus; and in diagnostic limitations, in that only a small portion of the large surface of the stomach was visible.

The flexible gastroscope came into being when it was learned that one could see through a curved tube if lenses of a very short focal distance were used. The instrument is 77 cm. long and 11 mm. in diameter, no larger in diameter than the large Ewald tube. Its advantage lies in the fact that when it is fully inserted there is an angle of deviation of 90° and an angle of vision of 85° so that one can see almost at right angles. The danger of perforation of the esophagus has been almost obviated because when fully inserted, the flexible

* Thanks are due Dr. Rudolf Schindler, of Chicago and Dr. Harold E. Wright, of Baltimore for their critical analyses of this paper.

portion is at least 3 cm. above the cardia where damage is most likely to occur. An instrument with an angle of vision of 45° is also made. Here the magnification is greater.

The survival rate of new clinical procedures is low. Survival depends on 4 considerations: (1) safety, (2) ease of accomplishment, (3) freedom from gross discomfort, and (4) production of results of value. As will be seen, gastroscopy has met all of these requirements.

1. *Safety.* Sixty gastroscopists performing 22,351 examinations in the United States, England and Australia reported to Schindler⁹ who inquired as to the safety of the procedure that there had been only one death. This followed perforation of the hypopharynx in a patient who had been bronchoscoped a week previously; this represents a mortality rate of 0.004%. There were also 8 perforations of the stomach and 1 perforation of the jejunum in a resected stomach, all with recovery. To this may be added 2 gastric perforations with recovery, 1 in 100 gastroscopies by Segal¹¹ and the other in more than 500 examinations by Schiff.⁷ These figures speak decisively for the relative safety of gastroscopy.

2. *Ease of Accomplishment.* The routine varies and in many places it is still unnecessarily elaborate. In my own hands simplicity has been the keynote. If there is no gastric residue, the patient may take food until 8 o'clock of the night preceding the morning of examination. When there is gastric residue, adequate aspiration and if necessary lavage must take place the night before. The only conditions in which gastroscopy should not be attempted are those involving the inability to pass the largest Ewald tube (11 mm.) easily into the stomach, aneurysms of the aorta and lesions of the esophagus: stricture, cardiospasm, cancer, varices. These, save for varices, can be determined by fluoroscopy alone and esophageal varices are almost never present except in the face of obvious hepatic disease. Therefore preliminary esophagoscopy is unnecessary. When dyspnea, cardiac decompensation, asthma, angina pectoris, esophageal diverticuli, kyphosis or scoliosis are present, the examiner must weigh their contraindications against the need of gastroscopy.

About 45 minutes prior to instrumentation the patient is given $\frac{1}{4}$ gr. of morphine and $\frac{1}{15}$ gr. of atropine. One-half hour after morphine and atropine, his tongue, buccal mucosa, gums, lips and pharynx are painted with 2% pontocaine hydrochloride by means of a curved camel-hair brush. Aspiration of the stomach contents is then performed, the large Ewald tube being used. The patient is then placed on an ordinary table on his left side with his left arm flexed under the left lateral aspect of the thorax. The knees are also flexed. Finally the instrument is inserted. Some examiners have a nurse or a technician hold the patient's head; this is not essential. As in cystoscopy, so in gastroscopy, the organ to be examined must be distended. In cystoscopy, the medium employed is water; in gastroscopy, the walls are separated by inflation with air. In short, the preliminary proceedings and actual technique are simple. The problem is not in the insertion of the gastroscope; it is in orientation and in interpretation which

require training and experience. Schindler's excellent monograph will be helpful in this connection.⁸

3. *Freedom From Gross Discomfort.* The examination is a matter of a few minutes. The use of the operating room is totally unnecessary. The ambulatory patient leaves a few minutes after the procedure without difficulty. He may have a sore throat which may appear after the anesthetic influence of pontocaine hydrochloride is no longer present, and it may persist for 12 to 24 hours. He is permitted to eat when anesthesia is no longer present, about 2 hours after its application, so that food, by virtue of the absence of the essential reflexes, will not pass into the trachea or bronchial tree.

4. *Production of Results of Value.* The question now arises as to what is to be gained by gastroscopy. Since it in no way rivals the Roentgen ray examination, is not expected to take its place, and is a complementary procedure, what does it add? This phase will now be discussed in association with the limitations of the procedure and the data procured by roentgenology.

Gastroscopy, like all other procedures, has definite limitations. Jankelson and McClure,² both excellent gastroscopists, have reminded us of these: gastroscopy visualizes only the mucosa; biopsy specimens cannot be obtained through the gastroscope nor has photography through it been perfected; small localized lesions may not be steadily seen due to changes in peristalsis and respiratory movements; lesions occurring with relative frequency and often malignant at the lesser curvature of the antrum are not always detectable by the gastroscope; there is difficulty at times in visualizing a niche on the lesser curvature of the upper third of the stomach; on occasion it may be impossible to distinguish between a benign or a malignant ulceration and between hyperplastic gastritis and cancer. Sometimes a stoma cannot be seen and a marginal ulcer on the jejunal side is missed. The distal portion of an hour-glass stomach cannot be inspected. There are a small group of patients temperamentally unfit for this procedure. These limitations in actual practice are not as formidable as they would seem. Since there is no perfect procedure, limitations are always to be weighed in relation to the ascertainable benefits. In the final analysis it is not what cannot be seen but what can be seen with this instrument that makes it so important. Experience and repeated examinations reduce some of these limitations. Those temperamentally unsuited for the procedure usually respond poorly to any other endoscopic or even more simple procedures. The use of pentothal sodium intravenous anesthesia may solve this problem.

Roentgen Ray Examination. Except in unusual circumstances, this should always precede gastroscopy. When is the latter to be instituted and what is to be expected of it in the presence of negative, positive, or inconclusive Roentgen ray findings?

1. *Negative Roentgen Ray Findings.* Gastroscopy is in order whenever the Roentgen ray findings are negative and there is a persisting suspicion of some abnormality. Whenever malignancy is a possibility because of such symptoms as discomfort with loss of weight or vitality,

anorexia, anemia and fever, this procedure is obviously indicated. A small number of malignancies and peptic ulcers may thus be detected. For instance, Lintott³ of Guy's Hospital in London reports that of 92 chronic gastric ulcers, 8 were encountered by gastroscopy which were negative by Roentgen ray, 2 were missed by gastroscopy which were seen by Roentgen ray and in all others there was agreement.

Roentgen ray is sometimes negative in the presence of hemorrhage. Undetermined hematemesis or melena may sometimes be explained by gastritis. Roentgen ray is not dependable in the diagnosis of gastritis, gastric analysis will not establish it and the gastroscope is the only reliable means of detection. In Germany it is stated that gastritis is responsible for 10% of all massive hemorrhages. There is some debate as to how soon gastroscopy is to be instituted following unexplained hematemesis or melena. My own practice is to do it just as soon as the initial shock is over. If one waits too long, acute lesions may be healed. Therefore, it is sometimes advisable to perform gastroscopy prior to roentgenology which is usually done a week or longer after hemorrhage.

Ill-defined complaints and a symptom-complex like that of duodenal ulcer will often be diagnosed as functional in character if the physical examination, roentgenology and other studies throw no light on structural change to account for them. Several types of gastritides have been found among this group since the advent of the flexible gastroscope. At this writing, it is not generally agreed as to the extent to which gastritis may account for complaints. Nevertheless it is important to know whether this condition is present or not. Some believe that atrophic and superficial gastritis frequently do not produce the digestive symptoms complained of, and here the patient as a whole must be treated rather than the gastritis. Even hypertrophic gastritis in some patients may never cause symptoms. These objective findings must be interpreted cautiously and in relation to the entire clinical picture.^{5,6}

Gastroscopy is further indicated in a small group of individuals who despite the usual assurances of the absence of structural change are unwilling to accept this in the presence of persisting symptoms. Negative gastroscopic findings enabling additional reassurances often puts them at ease.

2. *Positive Roentgen Ray Findings.* Even here, under certain circumstances, gastroscopy has its place. Not infrequently gross differentiation of benign lesions from malignant growths is made more correctly through the gastroscope than by Roentgen ray or at operation or from the gross resected tissue seen in the laboratory. For instance, Clerf and Wirtz¹ of the Jefferson Hospital in Philadelphia in a series of 34 patients with gastric cancer and gastric ulcer selected because the gastroscopic examination was essential in making a diagnosis, found that the Roentgen ray diagnosis in one patient was benign ulcer, in another malignancy was suspected and in the third no lesion was demonstrated by Roentgen ray; in each a diagnosis of carcinoma was made gastroscopically and verified histologically. The reason is

that through the gastroscope actual living tissue with undisturbed blood supply is seen. The appearance is different when the circulation is destroyed.¹⁰ I have heard urologists say that this situation is also true in cystoscopy, that the lesion and its gross differentiation is often better seen through the cystoscope than with the specimen in one's hand. These observations are not to be taken to mean that the final decision as between benign and malignant lesions is to be determined by its gastroscopic appearance. The appearances upon repeated examinations and the response to therapy may be the guiding factors. Obviously, the microscopic examination of the tissue offers the final word.

By Roentgen rays it is frequently difficult to differentiate spasm and edema associated with the lesion from the lesion itself; with the gastroscope the distinction may often be made more nicely. By gastroscopy one may be able to determine more clearly the question of operability; the decision may depend not only upon the site but also upon the extent of the involvement.

Even where duodenal ulcer is established by Roentgen ray but the clinical picture is atypical, gastroscopy is indicated because of the possibility of an associated gastritis. This manifestation is absent in a majority of such cases, but its presence should be known.

3. *Inconclusive, Incomplete and Inconsistent Roentgen Ray Findings.* Roentgen ray findings may not be conclusive in themselves or may be inconsistent in relation to the clinical picture. Gastroscopy is definitely indicated under these circumstances. For instance, when the Roentgen rays indicate an obstruction at the outlet of the stomach, it may be difficult to determine whether there is a lesion in the pyloric sphincter, in the duodenum, or in the gastric side of the sphincter. The location of the lesion is extremely important: if it can be localized to the first portion of the duodenum, it is almost certain to be benign; if it is in the pyloric ring, it may or may not be benign; if it is in the antrum, it is likely to be malignant. A normal pyloric ring, by gastroscopy, would be strong evidence in favor of a normal pyloric sphincter and with a normal antrum, the lesion could more readily be localized to the duodenum. At times, the typical clinical picture of uncomplicated duodenal ulcer may become modified; this may be due to gastritis demonstrable usually only by the gastroscope and the deformed duodenal bulb may be an indication of a previous ulcer. Frequently deformity without a persistent niche or crater is reported by Roentgen ray along the lesser curvature of the stomach. Is it active or it is scar tissue and are the symptoms on this or on another basis? The question can frequently be answered if visualization by gastroscopy can be made.

Those patients manifesting bizarre or atypical Roentgen ray filling defects and defects suspected of being extragastric should be gastroscopied with a view toward further clarification. Foreign bodies or polyps may sometimes best be detected by gastroscope.

Treatment of Benign Gastric Ulcer. The gastroscope has its place even here, for it is well known that the Roentgen ray indication of healing does not parallel the evidence obtained by the gastroscope.

The niche or crater may disappear in the roentgenogram within 2 to 4 weeks on medical management. The explanation is that inflammation and spasm account for much of the Roentgen ray defect which is often quickly corrected. However, epithelialization as noted by gastroscopy takes 6 to 8 weeks and sometimes longer. Hence no lesion demonstrable by the gastroscope should be considered healed unless this is evident by the gastroscope. This requires repeated gastroscopic examinations during the course of treatment.

Gastroscopy is Indicated Preoperatively and Postoperatively. 1. *Preoperatively.* It is necessary to ascertain whether in association with benign ulcer there is widespread gastritis, any additional ulceration or erosion not seen by Roentgen ray. While surgical intervention may relieve a not too extensive gastritis, it may also result in its exaggeration through altered anatomic and physiologic relationships. Hence such information is important for adequate evaluation of the problem. The differential diagnosis between benign and malignant lesions and the presence or absence of a lesion upon which an operation is planned has already been referred to.

2. *Postoperatively.* Any patient complaining of distress following gastric operations should be studied with the gastroscope following Roentgen ray examination. Roentgen ray under these conditions may sometimes be difficult of interpretation because of variations in the contour of the stomach incident to the operation and repair. Moershe and Walters⁴ found by gastroscopy, gastritis in 56 of 100 cases suffering from dyspepsia following various types of gastric surgery. No doubt a preoperative gastritis existed in some. In a majority with gastroenterostomy, the stoma can be viewed by gastroscopy; ulceration, gastritis and jejunitis if present can usually be demonstrated. Following subtotal gastrectomy for cancer or ulcer, recurrence of symptoms is an indication for gastroscopy in order to determine the presence of ulcer or gastritis or recurrence of malignancy, the earliest evidence of which may be detected by gastroscopy.

In general, gastroscopy is further indicated in all adults particularly over 40 complaining of ill-defined or mild digestive symptoms involving anorexia, loss of weight, nausea, vomiting, low grade fever and anemia. An early diagnosis of gastric malignancy may be made by this method.

Summary. Gastroscopy has become a permanent addition to our diagnostic armamentarium because of its safety, simplicity, the relative absence of gross discomfort and the production of results of value.

1. Gastroscopy is complementary to Roentgen ray in diagnosis.
A. When the Roentgen rays are negative and yet suspicion of abnormality persists, gastroscopy may reveal an occasional malignancy, erosions, peptic ulceration or gastritis. These lesions may also account for otherwise unexplained hemorrhage and a duodenal ulcer symptom-complex not due to duodenal ulcer.

B. When Roentgen rays are positive, gastroscopy makes possible: (1) confirmation; (2) a nicer gross differentiation between benign and malignant lesions; (3) a clearer delineation of the site and extent of the lesion which helps to determine the question of operability; (4) the

differentiation grossly of spasm and edema from the lesion itself; (5) the occasional detection of an associated gastritis which may account for atypical symptoms often erroneously ascribed to a Roentgen ray defect in the duodenal cap actually due to a healed, scarred ulceration.

C. When Roentgen rays are inconclusive, incomplete, inconstant, bizarre or atypical, gastroscopy may make possible: (1) a more accurate diagnosis of the presence or absence of a lesion; (2) the nature of a lesion responsible for an obstruction at the outlet of the stomach; (3) the presence of gastritis possibly accounting for a modification in the clinical picture of what would seem by Roentgen ray to be an uncomplicated duodenal ulcer.

D. In hemorrhage, gastroscopy may be instituted before acute lesions heal and prior to Roentgen rays.

2. Gastroscopy is often indicated preoperatively, even in the presence of positive Roentgen rays because it is desirable to know whether there is an associated gastritis or any additional ulcerations, erosions or masses not shown by the Roentgen rays.

3. Postoperatively: In gastro-enterostomy or in subtotal gastrectomy the return of any digestive complaints is an indication for gastroscopy. Ulceration, gastritis and jejunitis are usually readily detectable and the recurrence of a malignant lesion in the stomach may be first detected by gastroscopy. Here gastroscopy is particularly important because changes in the contour of the stomach incident to operation make roentgenologic interpretations difficult.

4. Gastroscopy is essential in determining the progression and healing of gastric ulceration.

5. Unexplained anorexia, loss of weight, nausea and vomiting, low grade fever and anemia are indications for gastroscopy. The earlier diagnosis of cancer may thus be made possible.

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MALIGNANT TUMORS IN PERSONS WITH CIRRHOSIS OF THE LIVER

BY SIGISMUND PELLER, M.D.

RESEARCH ASSOCIATE, DEPARTMENT OF ANATOMY, GRADUATE SCHOOL
NEW YORK UNIVERSITY, NEW YORK, N. Y.

RATS fed on a diet containing carcinogenic azo-compounds, especially hutter yellow, develop cirrhosis of the liver and hepatomas,^{2,8} unless the diet is enriched with a certain amount of bread, fresh liver, yeast,

or riboflavin and casein.^{3,4,9} These results revived the question whether and how dietary measures can be utilized in prevention of human cancer.⁵ A statistical analysis of the relationship between malignant tumors and cirrhosis in man seems, therefore, pertinent.

The postmortem records of the Bellevue Hospital, New York City, were studied for the period from March 1934 to February 1941. All cases over 20 years of age excluding those only partially examined were surveyed. There were 6596 cases; of them 4808 males and 1788 females.

Cirrhosis of the Liver. Cirrhosis was found 608 times (9.2%) in this series of autopsies. Of the cirrhotics, 37 men and 24 women had died in the age group 20-39 years, 221 and 84, respectively, in the age of 40-59 years, and 184 men and 57 women had died in the age group of 60 and more years. According to Table 1, the youngest age group, of the men examined postmortem 5%, and of the women 5.4% had cirrhosis; the corresponding figures in the middle age group were 9.8% and 11.6%, and in the highest age group 10.3% and 9.2%, respectively.

These figures refer to cirrhosis, regardless of whether or not this was the cause of death. In statistics of causes of death, cirrhosis appears in but $\frac{1}{7}$ or $\frac{1}{8}$ of our percentage.¹

For several reasons neither of both sources correctly pictures the frequency of cirrhosis in the population. In this series, 178 cases—29.5% of male, and 28.5% of female cirrhotics—were classified as early cirrhosis. Such cases remain undetected without autopsy, and may be in the general population more frequent than in our series. Furthermore, of the fully developed cases of cirrhosis a considerable portion die of other diseases, and thus enter the statistics of causes of death under various headings. In studying the relationship between cirrhosis and malignant tumors this has to be taken into account. On the other hand, even in a general hospital the necropsy material is a selection of cases, and thus cirrhosis may appear more frequently than is truly representative, and the proportions to other diseases may become distorted. One has to bear this in mind in order to omit improper conclusions.

In 473 cases a diagnosis of Laennec cirrhosis was made, 45 cases were designated as biliary cirrhosis, 10 as syphilitic, and 5 as fatty cirrhosis; in 75 cases no detailed classification was given.

Malignant Tumors of the Biliary System and of the Pancreas. As anticipated, malignant tumors of the liver appear in the cirrhotics much more frequently than in the remainder of the entire series of 6596 cases. Likewise, malignant tumors of the extrahepatic bile passages and of the pancreas occurred more frequently among cirrhotics.

Of 4365 males without cirrhosis, 17 ($0.39 \pm 0.08\%$) had a primary intrahepatic tumor,* while among 443 males with cirrhosis 18 ($4.06 \pm 0.93\%$) such cases were found. Male cirrhotics exceed the non-cirrhotics by 3.67 hepatic tumors per 100, with a critical ratio

* Of these tumors one was an angiosarcoma (in a 47-year-old negro), the remainder were carcinomas.

of 4, which is highly significant.* Adjusting the age distribution of cirrhotics to that of non-cirrhotics, one finds the crude rate of 4.06% to change to $3.94 \pm 0.93\%$ †. In women, the difference in intrahepatic malignant tumors is smaller; the corresponding values for 1623 non-cirrhotics being $5 \pm 0.31 \pm 0.13\%$, and for 165 cirrhotics $2 \pm 1.21\%$ (crude), and $1.08 \pm 0.81\%$ (age adjusted), respectively.

Out of the 20 cases of cirrhosis associated with intrahepatic carcinoma, 15 were classified as Laennec type, 3 as biliary, and 2 as cirrhosis without further specification. Of the 20 cases, only 1 (a female) was designated as early cirrhosis.

TABLE 1. MALIGNANT TUMORS OF THE LIVER AND OF INTRAHEPATIC BILE DUCTS

	20-39	Age at death, yrs.		Total
		40-59	60-	
Men without cirrhosis of liver:				
All cases	702	2032	1631*	4365
Tumor cases: No.	2	7	8	17
%	28	34	49	39
Men with cirrhosis of liver:				
All cases	37	221	185†	443
Tumor cases: No.	1	9	8	18
%	2.7	4.1	4.3	4.1
Women without cirrhosis of liver:				
All cases	419	642	562‡	1623
Tumor cases: No.		3	2	5
%		47	36	31
Women with cirrhosis of liver:				
All cases	24	84	57	165
Tumor cases: No.		1	1	2
%		1.2	1.75	1.2

* Among them 29 cases of unknown age.

† Among them 4 cases of unknown age.

‡ Among them 1 case of unknown age.

In the non-cirrhotic group, malignant tumors of the extrahepatic bile passages and pancreas were encountered 63 times, *c. g.*, in $0.89 \pm 0.10\%$ of males, and in $1.48 \pm 0.30\%$ of females; in the cirrhotic group—with 18 such cases—the corresponding age adjusted values are $2.66 \pm 0.77\%$ and $2.76 \pm 1.28\%$, respectively. In males the difference is considerable and 2.3 times the critical ratio, *c. g.*, statistically significant; in females the difference is smaller and insignificant.

Of the 18 cases of cirrhosis of the liver associated with a primary malignant tumor in the extrahepatic biliary organs or pancreas, 4 were classified as of the Laennec type (of them one early), and 14 as biliary cirrhosis (of them 6 early). In this group of tumors the portion of early cirrhosis is much higher than in persons with an intrahepatic malignant tumor.

Malignant Tumors of All Other Organs. Although there is a discrepancy between clinical observations and experimental results, cirrhosis has been persistently linked with chronic alcoholism.

* Critical ratio is the difference between two values divided by their standard error of the difference. A ratio of 2 and more is significant. A critical ratio of 4 indicates a probability of chance result as 1 in 16,000.

† Crude, *c. g.*, the actual percentage; age-adjusted percentage, *c. g.*, the figure as it would be in a group of cirrhotics of the age distribution of the non-cirrhotics.

In male alcoholics, malignant tumors of the mouth, pharynx, larynx, and esophagus are more frequent than in the general population.^{6,7} It is, therefore, of interest that of 443 male cirrhotics in this series 12 (*i. e.*, $2.71 \pm 0.70\%$) had a malignant tumor in one of these sites while the corresponding percentage in 4365 non-cirrhotics was $1.99 \pm 0.22\%$ (86 cases). The difference is statistically insignificant, indicating that for this purpose the material is too small to yield definite results. Of the 12 cases 2 had early cirrhosis.

TABLE 2.—MALIGNANT TUMORS OF EXTRAHEPATIC BILE PASSAGES AND OF PANCREAS

		Age at death, yrs.			Total
		20 39	40 59	60-	
Men without cirrhosis of liver:					
Tumor cases:	No.	1	17	21	39
	%*	14	83	1 28	89
Men with cirrhosis of liver:					
Tumor cases:	No.	..	4	9	13
	%*	..	1 81	4 86	2 93
Women without cirrhosis of liver:					
Tumor cases:	No.	1	5	18	24
	%*	24	78	3 21	1 48
Women with cirrhosis of liver:					
Tumor cases:	No.	..	2	3	5
	%*	..	2 38	5 26	3 03

* In per cent of all cases examined postmortem (see Table 1).

In males examined postmortem, no other group of organs shows an increased frequency of malignant tumors. Neoplasms of intestines are equally represented in both male groups, while in all other organs including stomach malignant tumors are found in $11.25 \pm 0.47\%$ of men free of cirrhosis, and in only $5.19 \pm 1.06\%$ of cirrhotics.

In females, tumors of the mouth, pharynx, larynx and esophagus are too rare for a statistical analysis. In this series there were altogether 10 such cases. As to the malignant tumors of other organs (see Table 3, Cols. 3-5), their percentages are smaller in those afflicted with cirrhosis, the difference being negligible as far as intestines and genital organs are concerned, a little larger with regard to the breast, and considerably larger in other organs. This difference is in women as well as in men highly significant, being 3.3 and 5.4 times the critical ratio, respectively.

TABLE 3.—MALIGNANT TUMORS IN VARIOUS GROUPS OF ORGANS (PER 100)

	Biliary system and pancreas Col. 1	Mouth pharynx, larynx and esophagus Col. 2	Intestines* Col. 3	Inner female genital organs Col. 4	All other organs† Col. 4	All organs Col. 5
Men without cirrhosis of liver:						
Of whole series	1 3	2.0	2.45	.	11.25	17.0
Men with cirrhosis of liver:						
Of whole series	7.0	2.7	2.5	.	5.2	17.4
Women without cirrhosis of liver:						
Of whole series	1.8	0.6	3.3	2.6	9.2	17.4
Women with cirrhosis of liver:						
Of whole series	4.2	..	3.0	2.4	4.2	13.9
Men with malignant tumor:						
Without cirrhosis of liver	7 5	11.7	14.4		66 4	100.0
With cirrhosis of liver	40.3	15 6	14.3		29 8	100 0

* From the duodenum to the anus.

† Including hematopoietic system.

TABLE 4.—MALIGNANT TUMORS IN ORGANS OTHER THAN BILIARY AND PANCREAS

	Age at death, yrs.			Total
	20-39	40-59	60-†	
Men* without cirrhosis of liver:				
No.	46	287	353	686
%†	6.6	14.1	21.6	15.7
Men* with cirrhosis of liver:				
No.	1	15	30	46
%†	2.7	6.8	16.2	10.4
Women* without cirrhosis of liver:				
No.	41	112	98	254
%†	10.5	18.0	17.5	15.6
Women* with cirrhosis of liver:				
No.	5	11	16
%†	6.0	19.3	9.7

* The total number of examined postmortem is given in Table 1.

† In per cent of all cases examined postmortem.

‡ Those of unknown age (see Table 1).

In the postmortem material the percentage distribution of malignant tumors does not correspond with that in the general population. Because of less interest in carcinoma of the stomach, in necropsies this type of tumor is less frequent, while lung tumors for instance are more often recorded. However, a carcinoma of the stomach combined with cirrhosis is not less interesting than one without cirrhosis. The same can be said with regard to leukemia, which are included in the malignant tumors. There were 36 males and 14 females who had leukemia among non-cirrhotics, but no case among cirrhotics.

Altogether, in persons free of cirrhosis, malignant tumors in organs other than biliary tract and pancreas are found with equal frequency in males and females (15.66%*). The crude as well as the age adjusted values for cirrhotics are much lower; 10.4 and $9.6 \pm 1.3\%$, respectively, for men, and for women 9.7 and $8.6 \pm 2.0\%$, respectively. Not all 3 age groups present the same relationship. As seen from Table 4, the difference in the frequency of malignant tumors changes inversely with age. For instance, in the 20-39-year old males, the difference between cirrhotics and non-cirrhotics is $6.6 - 2.7 = 3.9$, which is almost two-thirds of the value of 6.6%, while in the highest age group the corresponding figures are $21.6 - 16.2 = 5.4$, which is only one-quarter of the value of 21.6%.

Ratio of All Malignant Tumors. In the entire series there were 1125 cases of malignant neoplasm (17%); men having approximately the same ratio as women. As seen from Tables 3 and 5, in male cirrhotics the percentage of all malignant tumors is the same as in male non-cirrhotics, while in women there is a statistically insignificant difference in favor of the cirrhotic group. In the two younger age groups, malignant tumors are more frequently encountered in persons without cirrhosis; in the highest age group the relation is reversed.

The Race Factor. Of the 6596 cases of this series, 867† were colored, mostly negroes, Chinese and Japanese. On the average, at the time

* Without leukemia there were 14.84%.

† 559 men and 314 women.

of death, members of the colored races were 9 and 12 years younger, respectively, than whites. In colored persons cirrhosis of the liver was encountered in 9.1% of men, and in 4.8% of women; and malignant tumors were found in 12% and 12.1%, respectively. Higher mortality from tuberculosis and syphilis and death at younger age probably account for the lower ratios.

TABLE 5.—ALL CASES OF MALIGNANT TUMOR
Age at death, yrs.

	20-39	40-59	60-	Total
Men without cirrhosis of liver:				
No.	49	311	382†	742
%*	7 0	15 3	23 4	17 0 ± 0 6
Men with cirrhosis of liver:				
No.	2†	28	47	77
%*	5 4	12 7	25 4	17 4
Women without cirrhosis of liver:				(16 3 ± 1 7)§
No.	45	120	118	283
%*	10 7	19 25	21 1	17 4 ± 1 0
Women with cirrhosis of liver:				
No.		8	15	23
%*		9 5	26 3	13 9
				(12 9 ± 2 6)§

* In per cent of all examined postmortem (see Table 1).

† Both cases are colored.

‡ Among them 4 cases of unknown age.

§ Age-adjusted.

The association of cirrhosis and malignant tumor of the liver in colored men is more frequent than in whites. In 505 colored men without cirrhosis, intrahepatic malignant tumor was found only once, while in 48 with cirrhosis the combination was found 5 times. In the group of 3860 white non-cirrhotics intrahepatic tumor occurred 16 times, and in 395 white cirrhotics 13 times.

The number of colored women (15) having cirrhosis is too small to warrant generalizations. None of them developed a malignant tumor.

TABLE 6.—WHITES; MALIGNANT TUMORS IN VARIOUS GROUPS OF ORGANS PER 100
Organs

	Liver and intra- hepatic ducts Sub 1a	Extra- hepatic passages and pancreas Sub 1b	Mouth, pharynx, larynx, and esophagus Sub 2	Intestines from duodenum to the anus Sub 3	Inner female genital organs Sub 4	All other organs incl. hem- atopoietic system Sub 5
Men without* cirrhosis of liver	0 4	0 9	2 0	2 6		11 8
Men with† cirrhosis of liver	3 3	3 0	2 8	2 8		4 8
Women without‡ cirrhosis of liver	0 2	1 6	0 6	4 0	2 4	9 4
Women with§ cirrhosis of liver	1 5	3 5		3 5	3 0	4 7

All organs

	Crude	Age- adjusted
Men without* cirrhosis of liver	17 8	17 8
Men with† cirrhosis of liver	16 6	15 0
Women without‡ cirrhosis of liver	18 2	18 2
Women with§ cirrhosis of liver	16 2	15 0

* 3860 cases.

† 395 cases.

‡ 1332 cases.

§ 142 cases.

Restricting considerations to whites, one finds all the results obtained in the former analysis to be valid. In the age group 20-39 years, only

those without cirrhosis showed malignant tumors (7.6% of the men, and 10.6% of the women). In the middle age group, malignant tumors were encountered in non-cirrhotics in 15.8% (M) and 19.3% (F) respectively; and in 10.7% (M) and 11% (F) of cirrhotics. Within the highest age group, there is practically no difference in the percentage of malignant tumors between male non-cirrhotics (24%) and cirrhotics (23.3%), whereas cirrhotic women have a higher percentage of malignant tumors (27.7%) than non-cirrhotics (22.5%). The values for all age groups taken together are demonstrated in Table 6.

Early Cirrhosis and Malignant Tumors. In 1125 persons with malignant tumor, and in 5471 persons free from it, cirrhosis was found in 8.9% and 9.3% respectively. Of 42 persons with intrahepatic tumor 47.6% had cirrhosis; of 81 cases with a tumor in the extrahepatic bile passages or pancreas 22.2% had cirrhosis; and of the remaining 1002 tumor cases only 6.2% exhibited this liver condition.

Of the 100 persons who had both a malignant tumor and cirrhosis, 34% had cirrhosis in an early stage; for the 508 cirrhotics without a malignant tumor the corresponding figure is 28.3%. The difference is insignificant. Dividing, however, the formerly mentioned group of 100 cases according to the primary site of the tumor we find considerable differences as to the percentage of early cirrhosis.

Of the 20 cases of intrahepatic carcinoma combined with cirrhosis, only one example was classified as early cirrhosis; and of the 12 cirrhotics with a tumor of the mouth, pharynx, larynx and esophagus, only 2 had cirrhosis in an early stage. On the other hand, in cirrhotics with a primary tumor in extrahepatic bile passages or pancreas, 7 out of 18 had early cirrhosis. Here, of course, one may assume that the tumor led to the development of cirrhosis, and that the death occurred too early. Still larger is the portion of early cirrhosis in those who had a carcinoma or sarcoma of the intestines—7 out of 16—or a primary tumor in one of the other organs. In this latter group, out of 34 cirrhotics 17 had an early cirrhosis. The mechanism involved in obstructive biliary cirrhosis does not explain the high proportion of early cirrhosis in the latter 34 cases.

As a whole, the group of 178 cases with early cirrhosis has a ratio of malignant tumors a little higher than is that of non-cirrhotics (19.1% as compared with 17%) or the ratio of persons with fully developed cirrhosis (15.3%). There are also differences in the distribution of the tumors according to the organ.

Simultaneous Multiple Tumors. Of 1025 cases of malignant neoplasm without cirrhosis 29 (2.8%) had at least two primary tumors. In 26 of these neither the biliary system nor the pancreas was involved. The 3 other cases presented a combination of primary neoplasms in liver and stomach, in pancreas and breast, and in pancreas and kidney. Among 100 cases of malignant tumor associated with cirrhosis, multiple malignant tumors were encountered twice (2%). In one, pancreas and the prostate were the sites of carcinoma, in the other tongue and skin of the nose.

TABLE 7.—PERCENTAGE DISTRIBUTION OF THE PRIMARY TUMORS

	Organ			All organs
	Biliary system, pancreas, mouth, pharynx, larynx, or esophagus Sub a	Intestines, or genital organs Sub b	All other organs Sub c	
1025 persons with tumor:				
Without cirrhosis . . .	17.8	19.8	62.4 ± 1.5	100.0
34 persons with tumor:				
With early cirrhosis . . .	29.4	29.4	41.2 ± 8.4	100.0
66 persons with tumor:				
With fully developed cirrhosis	60.6	14.9	24.5 ± 2.8	100.0

Discussion. It will be recalled (Table 6) that of 100 non-cirrhotic males 17.8% had a malignant tumor, and of 100 cirrhotic males only 16.6%. This difference is statistically insignificant. There are, however, in this table 2 groups of organs with significant differences. In one group, sub 1, cirrhotics have a higher percentage of malignant tumors, while in the other, sub 5, cirrhotics have a considerably lower percentage of tumors than non-cirrhotics (4.8% as compared with 11.8%). Since this difference is found in all 3 age groups, it is not accounted for by premature death, and has to be explained in another way.

Does the value of 4.8% indicate a real deficit in the incidence of these tumors? In other words, do 1000 cirrhotics taken at random from the general population and followed until death have an incidence of malignant tumors in these "other organs" (Table 6, sub 5) smaller than have 1000 non-cirrhotics of the same age, sex and color? The answer depends on the frequency with which cirrhosis is responsible for the death.

An example may clarify the issue. Suppose that within a certain time, of 1000 cirrhotics 80 will die free of a malignant tumor, 10 will succumb to a tumor of one of the organs enumerated in Table 6, sub 1 to 4, and 10 will die of a tumor of one of the "other organs." Let us furthermore suppose that for 1000 non-cirrhotics the corresponding values are 50, 2, and 10 respectively. Under these circumstances, the incidence of tumors of an organ listed sub 5 of Table 6 is equal for both, cirrhotics and non-cirrhotics, namely $10/1000 = 1\%$. Nevertheless, dealing only with those who died, one is likely to overlook that equality, since of 100 deaths in the cirrhotic group $\frac{10}{80 + 10 + 10} = 10\%$ were due to malignant tumors of one of the "other organs," while the corresponding figure for non-cirrhotics is higher, namely $\frac{10}{50 + 2 + 10} = 16.1\%$. In this mock example, the incidence of malignant tumors of the stomach, the kidney, the lungs, the bladder, prostate, breast, thyroid, hematopoietic system, etc., would be just as high in cirrhotics as in non-cirrhotics, although in the total of deaths of cirrhotics these malignant neoplasms occupy a smaller percentage.

Before drawing conclusions from our actual figures, two values have to be estimated. First, one has to know how much the non-cancerous

mortality of non-cirrhotics is exceeded by that of cirrhotics; secondly, how high this excess would have to be in order to make the percentages sub 5 of Table 6 compatible with an undiminished incidence of these tumors within the total group of cirrhotics in the general population.

About the first point no data exist. Cirrhotics may have a surplus mortality on account of the cirrhosis, and on account of other non-cancerous diseases complicated by cirrhosis. In our postmortem series, 9.2% had cirrhosis, while in the Metropolitan Life Insurance statistics of causes of death¹ the corresponding figure is but one-seventh of this percentage. This indicates for cirrhotics an excess mortality due to cirrhosis of approximately 14%. The excess mortality due to the aggravation of other diseases cannot be calculated at all; only guessing is possible. Furthermore, in the general population the percentage of cirrhotics, especially of those with a fully developed cirrhosis may be somewhat smaller than in the postmortem series. These two factors, just mentioned, may account for an increase of the above calculated figure of 14% to about twice that value, or even a little more. This is a rough estimate.

On the other hand, we are able to calculate that the mortality of cirrhotics of all age groups would have to exceed that of non-cirrhotics by at least 82% in men, and 62% in women, in order to make the diminished ratio of tumors in "other organs" (see Table 6, sub 5) compatible with an undiminished incidence of these tumors per 1000 cirrhotics in the total population. Within the age groups of 20-59 years the discrepancy would be much larger. Furthermore one should bear in mind that the changes in the distribution of malignant tumors by site and the diminished ratio of tumors in the "other organs" are not limited to the fully developed cases of cirrhosis. We found them also in the group of 178 cases of early cirrhosis (Table 7), where this disease hardly is causing any excess mortality.

Thus we arrive at the conclusion that in cirrhotics the incidence of tumors in the stomach, kidney, bladder and prostate, lungs, breast, thyroid, hematopoietic tissue, etc., is lower than in non-cirrhotics. It is a real deficit, due to the increased frequency of malignant tumors in other organs in cirrhotics. This finding is in keeping with our results obtained in the analysis of other carcinogenic factors, regardless whether they do, or do not, deteriorate general health.^{6,7}

Summary and Conclusions. 1. In necropsy records of 6596 persons over 20 years of age, cirrhosis of the liver was found in 9%, and malignant tumors in 17%. About 30% of cirrhosis were classified as "early."

2. Compared with non-cirrhotics, persons with cirrhosis have a ratio of intrahepatic tumors several times increased; the ratio of malignant tumors in extrahepatic bile passages and pancreas increased to a smaller degree. Furthermore, male cirrhotics showed an increased ratio of malignant tumors of the mouth, pharynx, larynx and esophagus.

3. Cirrhotics have a much lower ratio of malignant tumors of all other organs taken together. The degree to which the ratio of tumors of all these "other organs" is diminished varies inversely with age.

4. Though increased general mortality is involved in bringing out

findings of paragraph 3, the second reason for the low ratio of malignant tumors of "all other organs" in cirrhotics is the actually diminished incidence of malignant tumors in this large group of organs. This is in keeping with our former investigations on the rôle of chronic irritation in human cancer.

5. Thus if by dietary or other measures cirrhosis of the liver could be prevented, the organ distribution of malignant tumors in human beings would change, but the total incidence of cancer scarcely would be reduced.

Grateful acknowledgment is made to Dr. W. C. Von Glahn, Director of Pathology of the Bellevue Hospital, for the permission to use the records.

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A CASE OF TOOTHPICK PERFORATION OF THE INTESTINES

BY W. ORR GOEHRING, M.D.

PITTSBURGH, PA.

(From Department of Surgery, Passavant Hospital)

INTESTINAL perforation by an ingested sharp foreign body seems to occur more commonly than the literature indicates.¹ McManus³ in 1941 was able to collect but 93 cases to which he added 2 of his own. He divided the perforating foreign bodies into 3 general groups: metallic bodies, 45 cases; animal bone, 39 cases; wood splinters, 9 cases. Included in the last group were several perforations due to a swallowed toothpick. Because of the rarity of perforation by such a commonly used object, the report of an additional case seems to be in order.

Case Report. W. L., a 63-year-old colored male, entered this hospital October 29, 1941, complaining of abdominal pain. He had been in good health until 10 days earlier when he noticed periodic cramp-like pain about his umbilicus. The pain was annoying but not disabling until 48 hours before admission when it became constant, more severe, and generalized. He then became nauseated and vomited; the pain and vomiting continued. His bowels had been normal. He had had no previous gastric symptoms. Except for lobar pneumonia in 1930, the past history was essentially negative. Physical examination revealed a slender male in acute distress, perspiring freely. The temperature was 100° F.; the pulse regular, 80 per minute; respiratory rate, 30. Significant findings were confined to a moderately distended and extremely tender abdomen. Maximum tenderness lay between the umbilicus and the symphysis. Rebound pain was marked. Peristalsis was absent. Roentgen examination on admission showed a small dilated loop of ileum in the right lower abdomen but no free air. The leukocyte count was 16,300 per c.mm. The red blood cell and hemoglobin determinations, blood chemistry values, and urinalysis were all within normal limits. The Kahn test was negative.

On conservative therapy, the patient's condition improved rapidly in the next 4 days during which time a grapefruit sized mass fixed to the abdominal wall developed in the lower mid-abdomen. Roentgen examination by barium enema showed a ptosed transverse colon adherent to the anterior abdominal wall at the site of the palpable mass. Incision and drainage was performed 12 days after admission and several ounces of thin purulent material were removed. The mass gradually decreased in size, while a small amount of drainage persisted. Intermittently, the patient gave evidence of partial small bowel obstruction. The appendix was at this time visualized by Roentgen examination as distinct from the mass. At operation under spinal anesthesia 36 days after admission, the abdominal wall sinus was found to communicate with an inflammatory mass the size of a hen's egg one end of which was connected to the mid-portion of the transverse colon, while the other end was connected to a loop of ileum adherent to the anterior abdominal wall just above the bladder, resulting in marked angulation of the bowel. This mass proved to be a foreign body granuloma containing a toothpick. Though it could not be definitely established, it was felt more likely from the findings that the toothpick had first penetrated the transverse colon and that the ileum had later impaled upon the toothpick. After excision of the mass, repair of the bowel walls and implantation of sulfanilamide in the abdominal cavity, the abdominal wall was closed. The patient was discharged 15 days post-operatively as cured. At no time could he recall having swallowed the toothpick, an interesting observation noted by others.^{2,3}

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STUDIES ON PROTHROMBIN

II. THE EFFECTS OF A SINGLE SMALL DOSE OF DICUMAROL* (3, 3' METHYLENEBIS [4-HYDROXYCOUMARIN]) IN LIVER DISEASE

BY SHEPARD SHAPIRO, M.D.

MILTON H. REDISH, M.D.

AND

HAROLD A. CAMPBELL, Ph.D.†

NEW YORK, N. Y.

(From the Department of Medicine, New York University and Third [New York University] Division, Welfare Hospital)

It has been observed that the same dose of Dicumarol (3, 3' methylenebis (4-hydroxycoumarin)) administered to different individuals may induce varying degrees of hypoprothrombinemia.^{2,3} Studies were undertaken to determine what might be the factors responsible for this variation.

As far as is known, Dicumarol acts chiefly on the prothrombin level (or activity).¹ That the liver plays an essential rôle in the elaboration

* Dicumarol is the collective trademark of the Wisconsin Alumni Research Foundation, which controls the use thereof.

† Present address: Central Laboratories, General Foods Corporation, Hoboken, N. J.

of prothrombin has been established.⁵ It appeared of interest, therefore, to investigate the reaction to Dicumarol of patients with liver disease.

The minimal single dose required to induce prolongation of the prothrombin time in 20 normal individuals was found to be 100 mg. It was decided to administer single doses of 50 mg. to a group of patients with liver disease. Sixteen were cases of Laennec's cirrhosis of the liver, one acute hepatitis, and one Wilson's disease.

TABLE 1.—EFFECT OF DICUMAROL ON PROTHROMBIN

Case No.	Initial prothrombin times		Initial prolongation	Maximal prothrombin times after 50 mg. Dicumarol		Response	Remarks
	Whole plasma (sec.)	12.5% plasma (sec.)		Whole plasma (sec.)	12.5% plasma (sec.)		
1	22.5	82.0	Marked	24.5	96.0	Pos.	History of spontaneous hemorrhages
2	20.0	78.0	Mod.	21.8	90.0	Pos.	Brain thromboplastin used
3	27.6	61.0	Mod.	29.0	76.0	Pos.	
4	19.0	60.0	Mod.	21.5	68.0	Pos.	Dicumarol given intravenously
5	18.2	62.0	Mod.	24.0	76.0	Pos.	Neg.
6	17.0	48.0	Sl.	17.2	59.1	Pos.	
7	14.0	52.0	Sl.	14.2	59.0	Pos.	Neg.
8	16.9	60.0	Mod.	18.4	76.0	Pos.	
9	17.0	44.5	Nor. (?)	16.8	41.5	Neg.	Neg.
10	15.0	42.5	Nor. (?)	16.8	42.5	Neg.	
11	17.6	49.5	Sl.	18.0	50.2	Neg.	Neg.
12	17.0	58.0	Sl.	17.1	59.9	Neg.	
13	17.2	44.2	Nor. (?)	16.8	45.5	Neg.	Neg.
14	15.4	46.0	Nor. (?)	16.5	48.6	Neg.	
15	15.8	47.7	Sl.	17.9	48.2	Neg.	Dicumarol given intravenously
16	15.1	60.0	Mod.	14.2	61.1	Neg.	Wilson's disease
17	15.4	45.2	Nor. (?)	15.5	45.0	Neg.	Dicumarol given intravenously
18	14.7	54.0	Sl.	17.0	72.0	Pos.	Acute hepatitis

NOTE: Lung thromboplastin used in all cases except Case No. 3.

Normal Standards

RABBIT LUNG THROMBOPLASTIN			RABBIT BRAIN THROMBOPLASTIN		
Whole Plasma	Arithmetic Mean	15 sec.	Whole Plasma	Arithmetic Mean	24 sec.
	Standard Deviation	±2		Standard Deviation	±2.3
12.5% Plasma	Arithmetic Mean	39.5 sec.	12.5% Plasma	Arithmetic Mean	41.4 sec.
	Standard Deviation	±2.5		Standard Deviation	±3.8

TABLE 2.—BLOOD VALUES BEFORE AND DURING RESPONSE TO DICUMAROL

Case No.	Date	Preexisting values				Date	Values during response to Dicumarol			
		Plasma, prothrombin time		Serum proteins, gm. per 100 ml.			Plasma, prothrombin time		Serum proteins, gm. per 100 ml.	
		Whole (sec.)	12.5% (sec.)	Total	Albumin		Whole (sec.)	12.5% (sec.)	Total	Albumin
2	5/16	20.0	78	6.81	4.52	5/19	21.8	90	6.95	4.56
3	5/16	27.6	61	6.07	4.08	5/19	29.0	76	5.98	4.22
5	5/16	18.2	62	6.14	3.04	5/19	24.0	76	6.80	3.27

Procedure. The method used for prothrombin estimation has been described by us.⁴ In this procedure, the prothrombin time of both whole and diluted (12.5%) plasma are estimated in duplicate.

Several prothrombin estimations were made in each case before the Dicumarol was administered, to establish the resting value for the prothrombin time of each subject. Fifty mg. of Dicumarol were then given either intravenously (4 cases) or orally. Blood samples were taken after 6, 12, 24 and 48 hours. In 7 cases additional specimens were obtained after 18 hours, and in 4 of these after 72 hours. The maximum prothrombin times obtained are recorded in Table 1.

The total serum proteins and albumin-globulin ratio, were determined in Cases 2, 3 and 5 before and during the interval when the prothrombin time was prolonged after Dicumarol (Table 2).

Discussion of Results. The mechanism whereby Dicumarol influences prothrombin is still obscure. In view of the importance of the liver in the elaboration of prothrombin, increased reactivity to Dicumarol in cases with hepatic functional derangement is significant.

Only 4 of the cases with liver disease showed prolongation of the whole plasma prothrombin time, while 7 showed a marked or moderate* prolongation of the diluted (12.5%) plasma prothrombin times and 6 cases showed a slight prolongation of the diluted plasma prothrombin time.

The prolongation of the preëxisting plasma prothrombin time is tentatively considered as a measure of the insufficiency of the prothrombin elaborating function of the cirrhotic liver. Consequently, the 5 cases showing normal prothrombin times will be considered as having normal liver function in respect to prothrombin elaboration and reactivity to Dicumarol.

All of the cases of cirrhosis of the liver and the single case of acute hepatitis, which showed an initial marked or moderate prolongation in the diluted plasma prothrombin time showed a definite response to 50 mg. of Dicumarol. Of the 6 cases which showed a slight prolongation of the diluted plasma prothrombin time, 3 responded to 50 mg. of Dicumarol. Cases with normal prothrombin time did not respond to this small amount of Dicumarol, nor did the 1 case of Wilson's disease, although the initial diluted plasma prothrombin time was moderately prolonged. It appears unprofitable therefore, to pursue the investigation further as a measure of the functional capacity of chronic cases of Laennec's cirrhosis of the liver.

As noted above, we have found that the prothrombin times of normal individuals does not increase after the administration of a single dose of 50 mg. of Dicumarol. Consequently, this investigation indicates that in Laennec's cirrhosis the subject responds to smaller quantities of Dicumarol than does the normal individual only when the disturbance in the liver causes prolongation of the prothrombin time.

The cases of liver disease responding to 50 mg. of Dicumarol showed the first detectable prolongation of the prothrombin time in the period of 12 to 24 hours after administration of Dicumarol. The latent period is of the same duration as that experienced when normal individuals are given an effective dose of Dicumarol. The character and duration of the response obtained by feeding 50 mg. of Dicumarol to cirrhotics is similar to that observed in normals after larger doses. The response usually involves a latent period followed by periods of depletion, plateau, and finally, restoration to the initial prothrombin time.

* Marked prolongation = Diluted plasma prothrombin time approximately twice normal.

Moderate prolongation = Diluted plasma prothrombin time between approximately $1\frac{1}{2}$ and twice normal.

Slight prolongation = Diluted plasma prothrombin time less than $1\frac{1}{2}$ times normal.

The total serum proteins and the A/G ratio were not measurably altered during the interval when the hypoprothrombinemic effect of Dicumarol was manifest.

The data presented here are significant in the therapeutic application of Dicumarol. It is fundamental that the prothrombin time be determined before the dosage of the anticoagulant is outlined. It appears also that the greater sensitivity of the method used here for the estimation of prothrombin time, makes it preferable to those in which only whole plasma is examined.

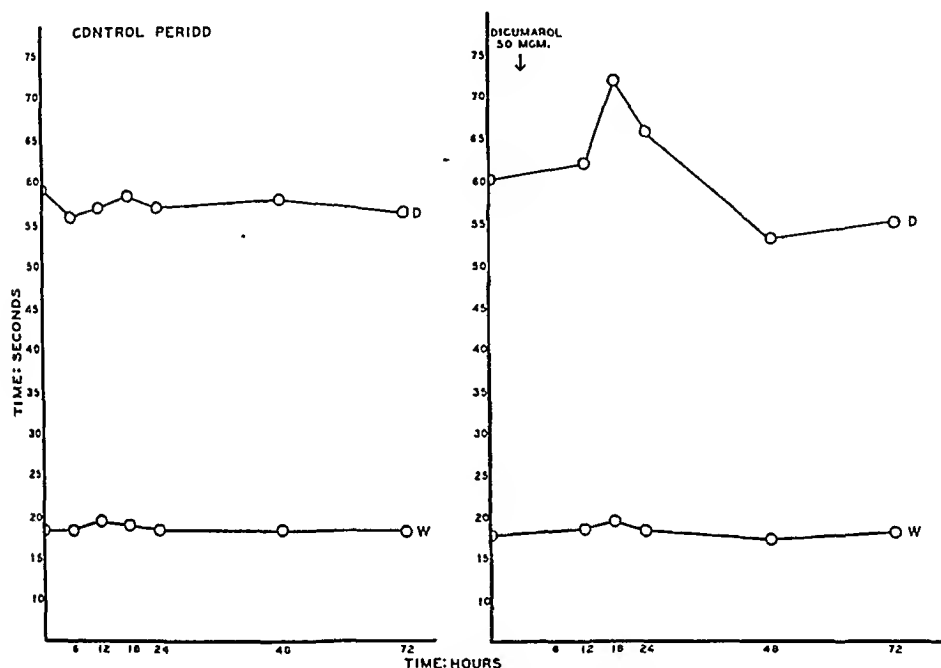


CHART 1.—Prolongation of diluted (12.5%) plasma prothrombin time after 50 mg. Dicumarol. The whole plasma prothrombin time is unaltered. Note overcompensation after prolongation.

Summary. Fifty mg. of Dicumarol (3, 3' methylenebis (4-hydroxycoumarin)), one-half the minimal dose found to induce a detectable prolongation of the prothrombin time in normal individuals, was administered to 18 patients with liver disease and with hypoprothrombinemia of varying intensities. All of the cases of Laennec's cirrhosis with marked or moderate preëxisting prolongation of the diluted plasma prothrombin time showed a definite response to the smaller dose of Dicumarol. Of 6 cases with slightly prolonged diluted plasma prothrombin time, 3 showed further increase, while no case with initial normal prothrombin time responded to the 50 mg. dose of Dicumarol. In those in which prolongation did occur the time of the first detectable change was the same as in normal individuals.

We wish to thank Dr. Arthur J. Patek, Jr., for making available to us for study several cases on the First Medical Division, Welfare Hospital. The protein determinations were done by Miss Yetta Porosowska. Miss Frances Kaufman gave technical assistance. The Dicumarol was supplied by Dr. K. K. Chen of Eli Lilly & Co. This work was aided in part by a grant from the Arlington Chemical Company, Yonkers, N. Y.

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PRODUCTION OF CYSTS FOLLOWING INTRAMUSCULAR INJECTION OF VEGETABLE OILS

By ROBERT C. PAGE, M.D.

AND

EDWIN J. DE BEER, PH.D.

TUCKAHOE, N. Y.

(From the Burroughs Wellcome & Co., U. S. A., Experimental Research Laboratories)

It has long been known that the intramuscular injection of oils may result in the formation of cysts or tumors.^{1-7,9} Sevringhaus⁸ has pointed out that the use of an oily medium for the intramuscular injection of endocrine preparations and certain drugs is not unattended by danger. However, in spite of the fact that this method of administration is widely used, the literature cites relatively few instances of untoward effects.

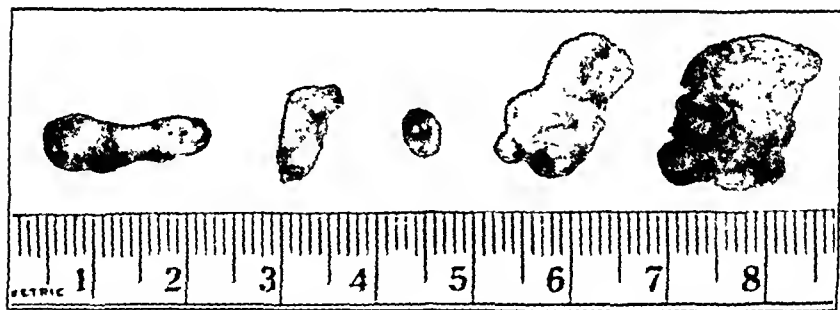


FIG. 1.—Photograph showing cysts as removed by dissection from rats following intramuscular injection of vegetable oils. From left to right the cysts are: unilocular cyst from sesame oil; multilocular cyst from corn oil; thin-walled unilocular cyst following olive oil; multilocular cyst with large amount of connective tissue following peanut oil; many small cysts in mass of tissue following injection of sesame oil and ether.

The present study was undertaken in order to determine which of a group of 5 common vegetable oils was most innocuous. The effects of reducing the viscosity of the oil by a mixture with ether was also studied.¹⁰ The 5 oils selected were corn oil, U.S.P., cottonseed oil, U.S.P., olive oil, U.S.P., sesame oil, U.S.P., and 2 samples of high grade peanut oil. A series of oil-ether solutions was also prepared by mixing 6 parts of the oil with 4 parts of diethyl ether, U.S.P.

Methods. All of the solutions to be injected were sealed in ampules and autoclaved at 15 lbs. pressure for 20 minutes. The oils were injected into the muscles of the right thigh of adult albino rats. The corresponding oil-ether solution was injected into the left thigh. All doses were 0.5 cc. Five animals were used for each kind of oil, except that only 2 were used with peanut oil (B). Altogether a total of 27 rats were used, each receiving 2 injections. One animal of each group was killed and autopsied at the following time intervals after injection: 4, 11, 18, 25, 32, and 40 days.

TABLE 1.—APPEARANCE OF CYSTS AT VARIOUS INTERVALS AFTER INJECTION OF FIVE OILS WITH AND WITHOUT ETHER

Days elapsed after injection	Corn oil	Corn oil and ether
11	Several multiloc. (4 mm.)*	Many multiloc., thin walls (1-2 mm.)
18	One large (4 mm.), many sm. (1 mm.)	Few sm. (1 mm.)
25	Multiple (1-5 mm.)	Sev. (1-2 mm.); soft fat-like tissue around injection site; inflam. fat with necrosis and perivascular deposition of calcium
32	Few sm. cysts (1 mm.); thick walls; mod. amt. chr. inflam. reaction	Sev. (2-4 mm.); thick walls; marked chr. inflam. reaction
40	One large (5 mm.); sev. sm. cysts (1 mm.)	Three thin-walled (1 mm.)
	Cottonseed oil	Cottonseed oil and ether
11	None; oil in musele	None; oil in musele
18	None; oil in muscle	Sm. multiple (1 mm.)
25	Many (1-4 mm.)	Many (1 mm.)
32	One large (6 mm.); sev. small (1 mm.); eos. in intercytic tissue	Several large (2-3 mm.); many sm. (1 mm.); marked chr. inflam. reaction
40	One (4 mm.); sev. (1 mm.)	Many sm. adj. (1 mm.)
	Olive oil	Olive oil and ether
11	Sev. multiloc. (1 mm.)	Sev. (2-4 mm.)
18	Many thin-walled (2-4 mm.)	Few thin-walled (1-3 mm.)
25	Mult. sm. (1-2 mm.)	Few (1 mm.)
32	Mult. (1-1.5 mm.)	Few sm. (1 mm.); widely separated; thin walls
40	One ovoid (2 x 2 x 3 mm); thick walls	Many (1 mm.)
	Sesame oil	Sesame oil and ether
11	Sev. multiloc. (2-4 mm.)	None; oil in muscle
18	Mult. (2-4 mm.)	Many thin-walled (1-3 mm.)
25	Several large (2-4 mm.)	Many sm. (1-2 mm.)
32	One large (6 mm.); few sm. (1 mm.)	Many sm. (1 mm.); marked chr. inflam. reaction
40	Several (3 mm.)	No oil found
	Peanut oil (A)†	Peanut oil (A) and ether
11	Sev. multiloc. (2-4 mm.)	None; oil in muscle
18	Many thin-walled (2-4 mm.)	Few thin-walled (1-3 mm.)
25	Sev. sm. thin-walled	Sev. (2-4 mm.)
32	Mult. sm. thin-walled (1-1.5 mm.)	None
40	One (1 mm.)	Four (1-2 mm.)
	Pennut oil (B)†	Peanut oil (B) and ether
7	Three (1.5-3 mm.)	One large intramusc. septa
21	Two large (4-5 mm.); sev. adjacent (1 mm.); fatty tissue adjacent	Sev. sm., multiloc. (1 mm.)

* Dimensions expressed in mm. (millimeter) refer to the average approximate diameter of the cysts.

† Two different samples of peanut oil were used.

Results. Translucent cysts filled with oil were generally formed by all 5 oils and by all of the oil-ether solutions (Table 1). In number

and size they ranged from many small, thin-walled cysts to 1 or 2 cysts as large as 6 mm. in diameter (Fig. 1). In only 7 out of 54 possibilities were no cysts found. In the 7 scattered instances in which oil but no cysts were found, the cysts may have been broken during dissection since they were generally thin-walled and quite fragile. These experiments indicate that there is little choice among these oils; all appear to produce similar cysts with equal frequency in rats.

As the experiment progressed no increases or decreases in the size, number or appearance of the cysts were observed.

Discussion. The oil-ether solutions produced less intercystic tissue, smaller cysts and in general the cyst walls were thinner. The oil-ether solutions also possessed the practical advantage of being much easier to inject. This was probably due to their lower viscosity. Since the total volume of oil and of the oil-ether solution injected was the same in each case (0.5 cc.) the actual amount of oil given in the oil-ether mixture was less. It seems doubtful that this fact would have any bearing on the results.

Summary. Cysts generally resulted from the intramuscular injection of the following vegetable oils: corn oil, cottonseed oil, olive oil, sesame oil and peanut oil and of oil-ether solutions in rats.

No indications were found that cysts became progressively smaller or larger, or changed in number or appearance with time.

No one oil appeared to be outstandingly better or worse than another oil in so far as cyst production was concerned.

The addition of ether to oil made injections easier and possibly decreased damage to the tissue.

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GALLOP RHYTHM—INCIDENCE AND THE INFLUENCE OF AGE, RACE AND SEX

By CURTIS F. GARVIN, M.D.

CLEVELAND, OHIO

(From the Department of Medicine of Cleveland City Hospital and the Western Reserve University School of Medicine)

GALLOP rhythm is a disorder of the heart beat characterized by the occurrence of 3 heart sounds during each cardiac cycle. Systolic gallop, in which the third sound occurs in systole, is rare and apparently

not of much clinical importance. Diastolic gallop rhythm, although not defined exactly the same way by all cardiologists, is considered uniformly to be of great clinical significance. It is with this type of gallop rhythm that this paper deals.

This study of gallop rhythm is based upon the clinical and pathologic records of 790 consecutive, adult patients who died of heart disease. These cases occurred in 6548 consecutive postmortem examinations done at Cleveland City Hospital in the decade from January, 1930, to December, 1939, inclusive. Gallop rhythm was present in 199 patients. The diagnosis of gallop rhythm was made clinically and was corroborated by phonocardiography only exceptionally.

The majority of the gallops seemed to be of the variety considered to be due to auricular contraction. In only 2 of the 199 patients with gallop rhythm was auricular fibrillation present. In these 2 cases the gallop presumably was due to a third heart sound, and no doubt in a few more instances this was the etiology of the gallop, although such cases appeared to be in the minority.

Discussion. *The Incidence of Gallop Rhythm in Various Types of Heart Disease.* Wolferth and Margolies² wrote that there were no quantitative data available as to the clinical incidence of gallop rhythm. They declared that there was no doubt that myocardial damage, both acute and chronic, predisposed to the development of gallop sounds. They considered that gallop occurred particularly in active rheumatic carditis, coronary occlusion, hypertensive cardiovascular disease, hyperthyroidism and anemia, and that it was very uncommon in patients with mitral stenosis.

The incidence of gallop rhythm in the various types of heart disease is shown in Table 1. It is seen that gallop rhythm occurs most frequently in hypertensive heart disease and coronary artery disease; 1 out of every 3 patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about 1 case in 5. Only 1 of 10 patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

TABLE 1.—THE FREQUENCY DISTRIBUTION OF GALLOP RHYTHM IN THE VARIOUS TYPES OF HEART DISEASE

Type of heart disease	No. of cases	No. with gallop rhythm	%
Hypertensive heart disease	264	93	35.2
Coronary heart disease	177	55	31.1
Rheumatic heart disease	119	12	10.1
Syphilitic heart disease	67	7	10.4
Cor pulmonale	54	10	18.5
Subacute bacterial endocarditis	31	2	6.4
Acute bacterial endocarditis	13	1	7.7
Thyroid heart disease	9	1	11.1
Calcific aortic stenosis	9	3	33.3
Obliterative pericarditis	7	0	0.0
Tuberculous pericarditis	7	4	57.1
Miscellaneous	14	3	21.4
Undiagnosed	19	8	42.1
	<hr/> 790	<hr/> 199	<hr/> 25.2

In relation to rheumatic heart disease, it is generally thought that gallop rhythm may readily occur in patients with active rheumatic carditis but that it is extremely rare in patients with well-developed mitral stenosis.² This idea is supported by this study. Of the 119 patients dying of rheumatic heart disease, 12 showed a gallop rhythm. Five of these 12 patients had acute rheumatic pancarditis. The remaining 7 showed various degrees and combinations of chronic rheumatic endocarditis, but in only 2 was there stenosis of the mitral valve (the entire series included 82 instances of mitral stenosis).

One of these patients with mitral stenosis and gallop rhythm was a 59-year-old white man who had severe arteriosclerosis of the coronary arteries with fibrosis of the myocardium. Coronary disease may have been a factor in the production of gallop rhythm in this case. The other was a 35-year-old colored female whose heart showed chronic rheumatic valvulitis of the mitral, tricuspid and aortic valves with stenosis of the mitral and tricuspid valves. No other explanation than the rheumatic heart disease was found to account for the gallop which had been heard by a number of observers.

In the other common type of valvular heart disease, syphilitic heart disease, gallop rhythm likewise is considered to occur uncommonly. In this study, of the 67 persons who died of syphilitic heart disease, 7 had gallop rhythm. But of these, 1 had complicating hypertensive heart disease, and 2 had complicating coronary artery disease (1 with recent myocardial infarction). In only 4 cases was there apparently no other explanation for the gallop than the syphilitic heart disease.

TABLE 2.—THE FREQUENCY DISTRIBUTION OF DEATHS OF PATIENTS FROM, 1, HYPERTENSIVE HEART DISEASE WITH GALLOP RHYTHM AND, 2, HYPERTENSIVE HEART DISEASE WITHOUT GALLOP RHYTHM

Age (yrs.)	Hypertensive heart disease with gallop rhythm	Hypertensive heart disease without gallop rhythm	Total
15-19	1	..	1
20-24	1		1
25-29	2		2
30-34	10	2	12
35-39	11	4	15
40-44	8	13	21
45-49	10	19	29
50-54	18	24	42
55-59	11	33	44
60-64	11	21	32
65-69	7	28	35
70-74	3	14	17
75-79	..	11	11
80-84	..	2	2
	93	171	264

Relationship of Age and Gallop Rhythm. The age in years at death of the patients who had hypertensive heart disease with and without gallop rhythm appears in Table 2. The average age at death of the patients with gallop rhythm was 49.5 years, the standard error being ± 1.3 . The average age at death of the patients without gallop rhythm

was 58.8 years (standard error ± 0.8). The standard error of the difference between these two averages is 1.5. The actual difference, 9.3 years, is 6.2 times this standard error, an indication that the difference is a highly significant one. It appears that it can be concluded that in fatal hypertensive heart disease, gallop rhythm is found in younger patients.

The age in years at death of the 55 patients with coronary heart disease and gallop rhythm, and the 122 patients without gallop rhythm appears in Table 3. The average for those with gallop rhythm was 57.3 years (standard error ± 1.4). For those without gallop rhythm it was 64.4 years (standard error ± 1.0). The standard error of the difference between these two averages is 1.8. The actual difference, 7.1 years, is 4.0 times this standard error, an indication that the difference is a highly significant one. Accordingly, it would seem that, on the average, in fatal coronary heart disease, patients with gallop rhythm are apt to be younger than those without gallop rhythm.

TABLE 3.—THE FREQUENCY DISTRIBUTION OF DEATHS FROM, 1, CORONARY HEART DISEASE WITH GALLOP RHYTHM AND, 2, CORONARY HEART DISEASE WITHOUT GALLOP RHYTHM

Age (yrs.)	Coronary heart disease with gallop rhythm	Coronary heart disease without gallop rhythm	Total
30-34	1	1	2
35-39	2	2	4
40-44	4	4	8
45-49	7	9	16
50-54	7	8	15
55-59	13	21	34
60-64	7	9	16
65-69	8	28	36
70-74	5	17	22
75-79	13	13
80-84	8	8
85-89	1	2	3
	<hr/> 55	<hr/> 122	<hr/> 177

The rarity of the simultaneous occurrence of gallop rhythm and auricular fibrillation (2 in 199 cases) has been noted. This means that the patients without gallop rhythm included almost all of the persons with auricular fibrillation. There is evidence¹ that the average age at death of cardiac patients with auricular fibrillation is greater than the average age at death of cardiac patients with a normal cardiac mechanism. This raises the question as to whether patients with gallop rhythm are younger merely because the control group contains so many persons with auricular fibrillation—persons who are apt to be older. Hence it seems advisable to compare the age of patients with and without gallop rhythm, but exclusive of those with auricular fibrillation.

The average age at death of 92 patients with hypertensive heart disease and gallop rhythm but without auricular fibrillation was 49.5 years (standard error ± 1.3). The average age at death of 115 patients with hypertensive heart disease and without both gallop rhythm and auricular fibrillation was 56.7 years (standard error ± 1.0). The stand-

ard error of the difference between these two averages is 1.6. The actual difference, 7.2 years, is 4.5 times this standard error, an indication that the difference is a highly significant one. It appears that it can be concluded that in fatal hypertensive heart disease, even excluding patients with auricular fibrillation, gallop rhythm is found in younger patients.

The age in years at death of the 54 patients with coronary heart disease and gallop rhythm but without auricular fibrillation was 57.4 years (standard error ± 1.4). For the 88 patients with coronary heart disease without both gallop rhythm and auricular fibrillation it was 62.2 years (standard error ± 1.2). The standard error of the difference of these two averages is 1.9. The actual difference, 4.8 years, is 2.5 times this standard error, an indication that the difference is significant. Accordingly it would seem that in fatal coronary heart disease, patients with gallop rhythm are apt to be younger than those without gallop rhythm, even excluding patients with auricular fibrillation.

Relationship of Race to Gallop Rhythm. The 264 patients with hypertensive heart disease consisted of 168 white and 96 colored patients. Of the 168 white patients, 53 (31.5%) showed a gallop; of the 96 colored patients, 40 (41.7%) had a gallop. Although the colored patients show a higher incidence of gallop rhythm than the white patients, the difference is not statistically significant.

There were 158 white and 19 colored patients who died of coronary heart disease. The 158 white patients included 47 (29.7%) with gallop, the 19 colored patients 8 (42.1%) with gallop. Again, the incidence of gallop rhythm is higher among the colored patients, but the difference is not statistically significant.

If the patients with hypertensive and coronary heart disease are grouped together (and it must be granted that the two types of heart disease not infrequently are associated), then of the 326 white patients, 100 (30.7%) had a gallop, while of the 115 colored patients, 48 (41.7%) had a gallop. This difference is found to be significant,* and it would appear that colored patients with hypertensive heart disease and/or coronary heart disease show a higher incidence of gallop rhythm than do white patients.

Relationship of Sex to Gallop Rhythm. The 264 patients who died primarily of hypertensive heart disease included 178 males and 86 females. Of the 178 males, 62 (34.8%) had a gallop, while of the 86 females, 31 (36.0%) had a gallop. The difference is not significant when tested by the chi square method.

There were 140 males and 37 females who died of coronary heart disease. Of the 140 males, 43 (30.7%) had a gallop; of the 37 females, 12 (32.4%) had a gallop, a difference which is not significant.

Apparently there is no relationship between sex and the occurrence of gallop rhythm.

* The term "significant" refers to a difference which could be produced by chance in less than 5% of trials as demonstrated by the chi square test.

Comment. An increased frequency of occurrence of gallop rhythm in younger patients, and colored patients has been demonstrated. The association between gallop rhythm and age is marked. The relationship between gallop and colored patients could be demonstrated only by combining the hypertensive and coronary groups.

It seems likely that the association between gallop and color is really a manifestation of the influence of age. In the hypertensive group, the average age at death of the white patients was 57 years, of the colored 50. In the coronary heart group, the average age at death of the white patients was 62.6 years, of the colored patients 53.9. Thus it is seen that in both groups the white patients were older. If white and colored patients of the same age grouping are compared, no association between gallop and color is demonstrable, although the groups are not sizable.

In regard to age, however, the relationship is definite and certainly not related to color. Thus, for example, in the hypertensive group, in the group of white patients only, a higher incidence of gallop in the younger patients is easily demonstrable.

Summary. Of 790 consecutive, adult autopsied patients dead of heart disease, 199 (25.2%) had had a gallop rhythm due either to auricular contraction or a third heart sound. Gallop rhythm occurred most frequently in hypertensive heart disease and coronary artery disease; 1 out of every 3 patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about 1 case in 5. Only 1 of 10 patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

The average age at death of 93 patients with hypertensive heart disease and gallop rhythm was 49.5 years, of 171 patients with hypertensive heart disease and no gallop rhythm 58.8 years. Patients with coronary artery disease and gallop rhythm (55) averaged 57.3 years at death; 122 patients with coronary heart disease and no gallop rhythm averaged 64.4 years. Both of these differences seem to be statistically highly significant. Even if patients with auricular fibrillation are excluded (such patients rarely have gallop rhythm and are apt to be older), it still appears that the average age at death of cardiac patients with gallop rhythm is less than the average age of cardiac patients without gallop rhythm.

If the patients with hypertensive and/or coronary heart disease are grouped together, of 326 white patients, 100 (30.7%) had a gallop while of the 115 colored patients, 48 (41.7%) had a gallop. This seems to indicate that colored patients with fatal hypertensive heart disease and/or coronary heart disease, show a higher incidence of gallop rhythm than white patients. It is thought that this is really a manifestation of the influence of age, for the average age at death of the colored patients was less than that of the white patients.

No association between gallop rhythm and sex was demonstrable.

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STUDIES ON THE EFFECT AND MECHANISM OF AMPHETAMINE
SULFATE ON WEIGHT REDUCTION*

BY RALPH H. KUNSTADTER

MAJOR, MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

H. NECHELES, M.D., PH.D.

Assisted by M. WEINER

CHICAGO, ILLINOIS

(From the Department of Gastro-intestinal Research and from the Children's Endocrine
Clinic, Michael Reese Hospital)

IN a previous communication, one of us described the use of amphetamine sulfate in the management of obese children and was impressed by the frequent suppression of appetite following the administration of varying doses of this drug.⁴

It is our feeling that this effect could not be attributed principally to suggestion, fear of the doctor or parent, or education and suggestion during regular clinic attendance, for the following reasons: Previous medication, including thyroid extract, ephedrine, etc., had failed to affect the appetite. (In many instances there was a return of appetite and gain in weight during substitution therapy with placebos or other drugs.) Parents were instructed not to nag or police the children but to use an attitude of indifference. In a later group a prescribed reducing diet was not used, the children being permitted to eat *ad libitum* and yet, during amphetamine therapy, appetite was reduced and weight loss resulted in most instances.

We have found that many children developed a rapid tolerance to the drug. Following initial weight loss on a given dose of amphetamine, appetite returned gradually, necessitating an increase in the dose. The increased dose usually resulted in a renewed depression of appetite and loss of weight. The failure to realize this fact may account for the poor results of others.

The mechanism for the loss of appetite and decrease in weight following the use of amphetamine sulfate is still obscure. Observations from our own and from other laboratories have shown that the drug inhibits motility and emptying of the normal human and dog's stomach.^{1,7} Apparently no studies on the effect of the drug on the normal hunger motility of the human stomach have been made. The effect of amphetamine sulfate on gastric secretion has been described as slight, insignificant, inconstant,⁸ and significant.⁶ No studies of the effects of amphetamine on psychic secretion were found in the literature. It is our purpose in this paper to present our clinical impressions and laboratory observations on the mechanism of action of this drug.

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It has been our clinical impression that under the influence of amphetamine sulfate, many of the children were more alert and exhibited greater physical activity, factors which in themselves could account for loss in weight. Recent observations have shown that the basal metabolic rate is not significantly increased by this drug.⁴

Another important feature is the ability of obese children treated with amphetamine sulfate to adhere to their diet with greater ease. Will-power seems to be definitely increased. This may be related to the effects of the drug on personality, on depressive and other abnormal mental states, on perversions of appetite, and on the emotional condition described by Lesses and Myerson as *anhedonia*.^{5*} We do not feel therefore, that favorable results obtained with such different methods as drug therapy on one hand and education, suggestion and psychiatry on the other, prove that the effects of drug therapy are due to the suggestions, education, etc., which is necessarily involved in regular clinic attendance. Amphetamine renders the patient more apt to external (self) discipline. The drug may be even more useful in a class of patients in whom psychiatric treatment can be detrimental.²

Methods. The studies on psychic secretion were carried out on dogs provided with a double-barreled esophagostomy and with a Pavlov pouch. The animals were shamfed with ground raw meat and water, and their secretion determined during and following this procedure. Then the animals were rested and, after a period of time, amphetamine sulfate was injected and the procedure of shamfeeding was repeated. In control experiments both tests gave similar values for volume and acidity.

Gastric secretion was studied in Pavlov pouch dogs, using the double histamine test. The drug was administered at the time of the second injection of histamine.

Gastric motility was studied with the stomach balloon method, using an oil-carbon tetrachloride (sp. gr. 1.5) manometer. In the human, a moderate degree of air inflation was employed and the normal, periodic hunger motility recorded. In the dog, the stomach balloon was distended to a degree which did not produce vomiting or discomfort of the animal. This distention was productive of continuous and vigorous gastric motility, which was useful and practical for the assay of the drug.

In all series of tests, controls were performed in which nothing, water or saline solution, was administered instead of amphetamine. No appreciable effects of the water or of the saline solution were noted.

Results. *A. Psychic Secretion* (2 animals). Chart 1 represents a typical experiment. Three and 5 mg. of amphetamine sulfate injected intravenously before the second shamfeeding did not materially affect the secretion of the Pavlov pouch. Larger doses of the drug could not be employed, because the animals lost their desire to eat readily.

B. Secretion of the Pavlov Pouch (3 animals). In the double histamine test, the effects of amphetamine sulfate were variable. In some experiments secretion was increased during the first 60 minutes, but in others there was no effect. The outstanding observation in these experiments was that the effect of amphetamine sulfate, if any, was transient. In positive experiments secretion reached its peak 60 minutes after

* For reference on this and other effects of amphetamine the reader is referred to the extensive *Survey of the Literature* published by Smith, Kline & French.

injection of amphetamine and the effect of the drug had completely disappeared at the end of 90 minutes. The total acid expressed in mg. of HCL was increased considerably in some experiments while in others there was no increase, although the curve showed a distinct rise 60 minutes after injection. This latter phenomenon was due to lower values before and after the peak.

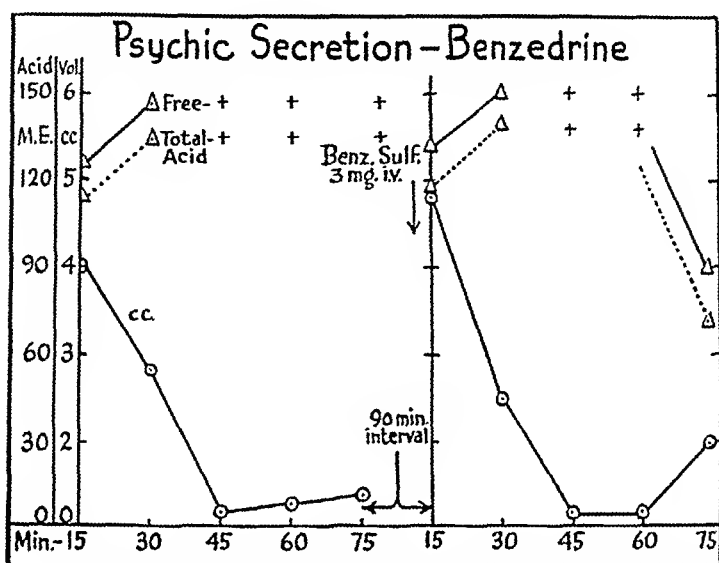
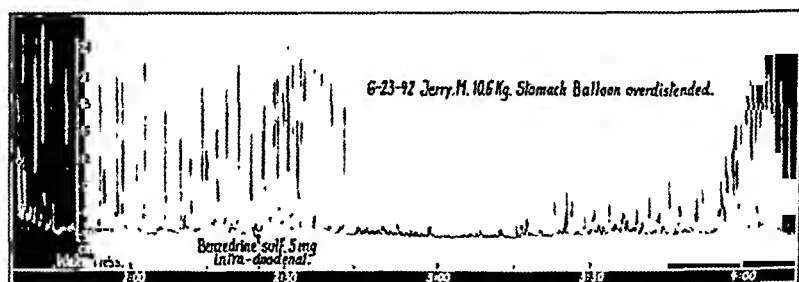


CHART 1.—Dog Lamar, 17.1 kg., male. 1-29-42. Amphetamine sulfate i.v. 30 minutes before second shamfeeding. The + signs indicate the presence of acid, but the volumes were too small for titration.



periods of time. Figure 1 represents a typical experiment. Figure 2 represents an atypical experiment of considerable interest. While in the typical tests a depression of gastric motility was followed by resumed continuous motility, in this animal the drug produced prolonged periods of rest alternating with relatively short periods of more or less strong motility.

Figure 3 represents a typical experiment in the human. The drug did not affect normal hunger motility prevailing at the time of injection. After this period of hunger motility had ended, however, the effect of the drug became apparent. The following period of rest was greatly lengthened, and when hunger motility returned, it was of low intensity and atypical for a number of hours.

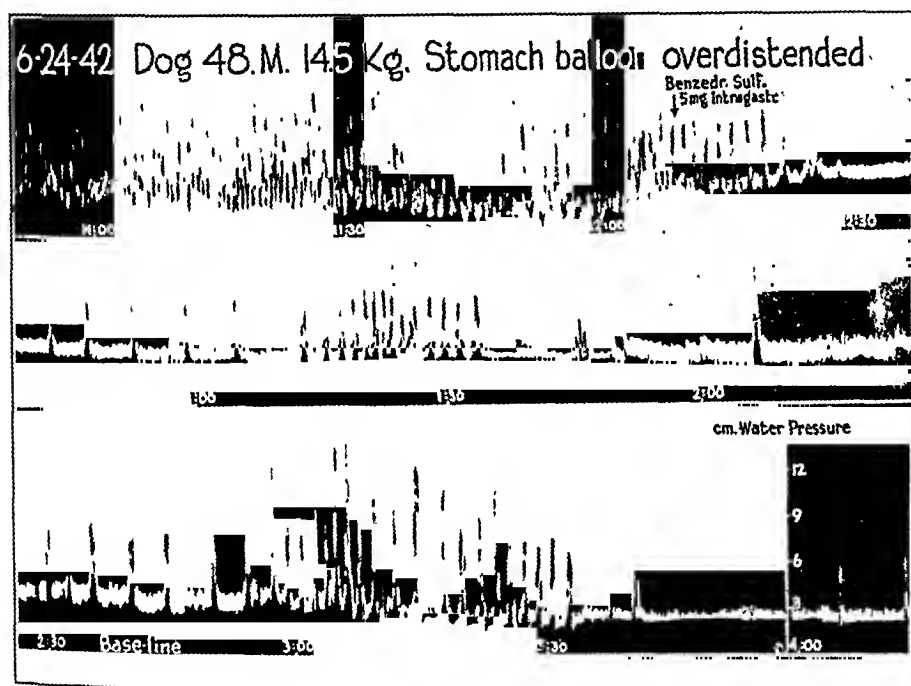


FIG. 2.—Dog unanesthetized, male, 10.6 kg. Continuous gastric motility from overdistention of stomach balloon. At arrow, 5 mg. of amphetamine sulfate in 5 cc. of warm water was administered through a thin catheter, introduced through the gastrotomy cannula. After a latent period of 22 minutes, periods of complete rest alternated with periods of single or repeated contractions; this lasted for about 2 hours, when the test was ended. Time is marked in half-hour periods.

Discussion. Amphetamine is regarded by many clinicians as a sympathomimetic drug, comparable to epinephrine in its biologic effects. This is not quite true, however,³ and Tainter has called it a pseudo-sympathicotropic drug.⁹ Dryness of the mouth is frequently observed in patients following administration of amphetamine. This latter effect is not observed with epinephrine, and may therefore be called atropine-like. It was chiefly this observation that made us feel that amphetamine might affect psychic secretion.

While our experiments in the dog show the absence of appreciable

change in psychic secretion following the drug, this need not be applied to the human. Whenever we are dealing with central nervous effects of drugs, the situation is much more complicated in the human than in any animal. We have not been able to extend the study to young subjects because of technical difficulties.

We cannot explain the variability of the responses of the Pavlov pouch of the same or of different dogs to the injections of amphetamine.

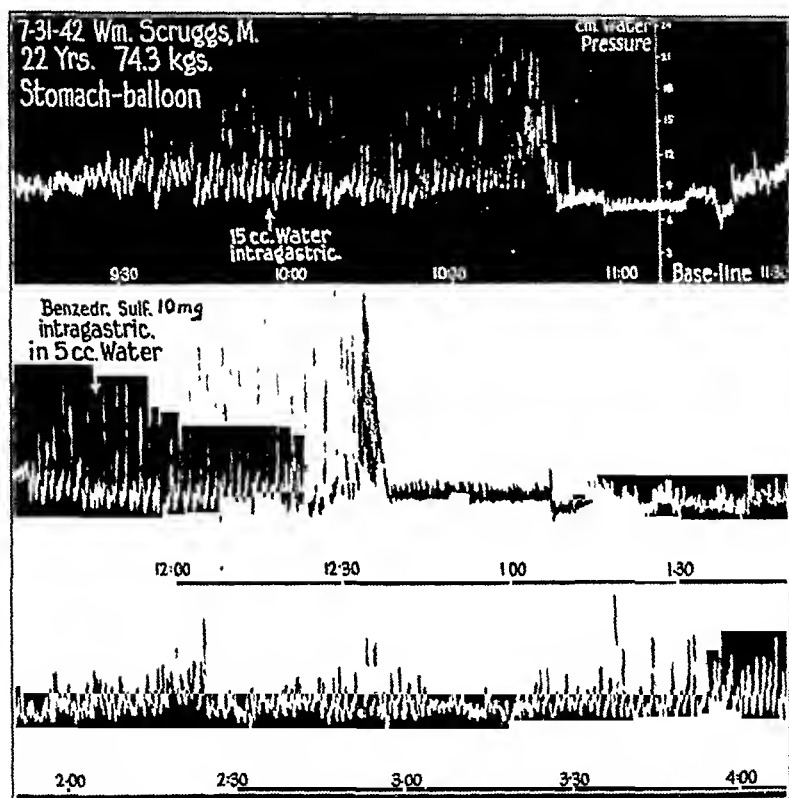


FIG. 3.—Human, 22 years, 74.3 kg. Normal, fasting, stomach balloon. Regular hunger motility. At first arrow, 15 cc. of warm water was injected as control into stomach through the second lumen of the balloon tube. At beginning of second period of hunger motility 10 mg. of amphetamine sulfate in 5 cc. of warm water was injected into stomach (second arrow). After a latent period of 50 minutes motility was more or less absent for 40 minutes and from then on (+2 hours) motility was weak, and no hunger pangs were felt by the subject. Time is marked in half-hour periods.

That is, we do not know why in some animals there is a slight increase, in others a large increase, and in still others no change at all in the secretion and acidity of gastric juice following the injection of histamine and of histamine and amphetamine. The total amount of mg. of HCL secreted was not greater in a number of experiments than in the controls, although it was distinctly greater in the 60-minute samples after injection of histamine and amphetamine.

The suppression of gastric motility in the dog and in the human following the administration of amphetamine either by mouth, intragastric or intraduodenal, or by intravenous injection, was distinct and prolonged in most experiments. Even in those tests in which motility was not abolished completely it was modified. Typical strong hunger contractions were absent but smaller contractions, not sufficient to evoke the feeling of hunger, prevailed. This group of experiments showed conclusively that amphetamine affects the feeling of hunger and probably reduces craving for food. The periods of inhibition appear to be sufficiently long to warrant the assumption that 3 doses of amphetamine per day will probably abolish more or less the feeling of hunger between meals.

We do not assume that the above described effects of amphetamine on hunger motility can explain entirely the reduction in appetite and the loss of weight following the administration of the drug to obese children, but we are inclined to believe, that the psychic effects mentioned before, contribute to a considerable extent.

Summary and Conclusions. The possible causes for the decrease of appetite and the loss of weight of obese children treated with amphetamine sulfate (Benzedrine) were analyzed.

The drug caused increased activity, and mental and physical responses were distinctly increased. The children appeared to be more disciplined under the influence of the drug, and followed their diet with greater ease. These effects were due to the drug rather than to education, "policeing" or suggestion during prolonged clinic attendance, because the children regained their appetites and weight when placebos or other drugs were administered.

In laboratory experiments the following results were obtained:

Psychic secretion in the dog was not materially changed by amphetamine sulfate.

The effects of amphetamine on gastric secretion of the dog were inconstant.

Gastric motility in the dog and in the human was depressed considerably following the administration of amphetamine.

It is believed that the psychic effects of amphetamine plus the depression of gastric hunger motility and of hunger can explain the results obtained by us in the treatment of the obese child.

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VACUUM DRIED HUMAN SERUMS IN THE PREVENTION AND
TREATMENT OF CERTAIN OF THE COMMON COM-
MUNICABLE DISEASES—AN 8-YEAR STUDY

By AIMS C. MCGUINNESS, M.D.

ASSOCIATE IN PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

JOSEPH STOKES, JR., M.D.

PROFESSOR OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

AND

JANET G. ARMSTRONG, R.N.

ASSOCIATE DIRECTOR, PHILADELPHIA SERUM EXCHANGE
PHILADELPHIA, PA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania,
and The Children's Hospital of Philadelphia)

PREVIOUS reports^{11,12,13,15} have described the clinical use of human serums dried *in vacuo* from the frozen state for the preservation and treatment of certain infectious diseases in relatively small groups of patients. The present report presents the results obtained with such serums over an 8-year period in the prevention of measles, mumps, and chickenpox, and in the prevention and treatment of scarlet fever and whooping cough.

Because febrile and shock type reactions, to be discussed later, occasionally occurred following their intravenous injection in the early years of this work, vacuum dried serums in the present studies were at first used only for intramuscular injection. It now appears that the intravenous injection of vacuum dried serums prepared by the newer techniques is probably as innocuous as the intravenous injection of the same serums prepared in the liquid state.

In view of the fact that these serums may be restored in a small fraction of their original water content, for routine intramuscular use, it has been customary to dissolve the powdered residue from each 10 cc. of serum in 4 cc. of sterile distilled water. This markedly reduces the bulk of the material to be injected; *e. g.*, 20 cc. of serum may be injected as a total fluid volume of 8 cc. For intravenous injection the serum may be restored to its original volume if so desired.

Preservatives have not been added to such serums in the desiccated state, but serum centers operating under license from the National Institute of Health are required to supply with each ampule of desiccated serum an ampule of sterile distilled water containing 0.35% phenol. The purpose of this procedure is to prevent the contamination of such serums following restoration to the fluid state.

Measles Prophylaxis. Both convalescent and normal pooled adult serums have been employed in passive immunization against measles. Particular interest has been paid to the use of vacuum dried normal adult serum in pools containing the bloods of a minimum of 50 individual donors inasmuch as convalescent serum is extremely difficult to obtain in sufficiently large quantities to be of general practical value. Moreover, it is felt that the use of large pools of normal serum

provides a product which varies little from pool to pool whereas small pools or individual bulks of convalescent serum undoubtedly vary tremendously in their protective power. The disadvantage that somewhat larger doses are required when pooled adult serum is employed is offset to a large extent by the advantage that vacuum dried serums are generally concentrated to less than one-half their original volume when restored to the liquid state.

Results comparable to those described here have been reported with the use of liquid pooled adult serum by Gunn,⁶ Lempriere,¹⁰ Champlattou,³ Bull,² and others; the latter two studies were well controlled. Likewise, the results obtained with vacuum dried convalescent serum are quite comparable to those reported in many studies with liquid serum beginning with those of Nicolle and Conseil¹⁴ in 1918.

TABLE 1.—MEASLES PROPHYLAXIS VACUUM DRIED HUMAN SERUM (1233 CASES)

	Convalescent serum 168 cases			Pooled adult serum 1065 cases		
	No disease	Attenua- tion	Disease	No disease	Attenua- tion	Disease
Close exposure (desired result often attenuation)	77	40	5	471	273	18
Casual exposure (including hospital)	37	6	3	267	25	11
			Convalescent serum	Pooled adult serum		
<i>Dosage Schedule for Complete Protection:*</i>						
Age 6 years or under			10 cc.†	15-20 cc.		
Age over 6 years			15 cc.	20 cc.		
Age over 12 years			15-20 cc.	30 cc.		

*Dosage Schedule for Attenuation:** Give one-half the dose recommended for complete protection in the first 3 days following the initial exposure. Give two-thirds of the dose recommended for complete protection on the 4th or 5th days following the initial exposure, and the full dose recommended for complete protection on the 6th and 7th days following the initial exposure.

* After the 7th day following exposure, the value of serum is questionable.

† 4-5 cc. diluent used for each 10 cc. of original serum.

The results obtained in measles prophylaxis with both convalescent and pooled normal adult serum are shown in Table 1. The suggested dosage schedule is also given in this table. It will be noted that the cases are divided into a group given serum after close exposure, and a second group whose exposure was casual (including ward exposures). Obviously the expected secondary case rate is much higher following a more intimate exposure.

The results are indicated as "no disease," "attenuation," and "disease." Obviously, the desired result is "attenuation," except in the instance of ward and other institutional exposures where it is important to prevent the spread of an epidemic and in certain very young and delicate children. A case of measles is considered attenuated if fever lasts for no longer than 24 to 48 hours and there are no complications. In general, it is felt that serum administered later than the 7th day following the initial exposure has little effect in modifying or preventing the disease. If either convalescent or pooled adult serum is given in adequate amounts sufficiently early in the incubation period, complete

protection or attenuation will follow in 90% or more of the cases injected.

TABLE 2.—SCARLET FEVER PROPHYLAXIS VACUUM DRIED HUMAN SERUM (1195 CASES)

	Convalescent serum 1043 cases		Pooled adult serum 152 cases	
	No disease	Disease	No disease	Disease
Close exposure . . .	551 (238)	22 (7)	102 (57)	5 (2)
Casual exposure (including hospital) . . .	170 (106)	0	45	0

Figures in parentheses indicate number of cases known to be Dick positive.

*Dosage schedule:**†

Age 6 years or under

Age over 6 years

Age over 12 years

Convalescent serum

10-15 cc.‡

15 cc.

20 cc.

* For pooled adult serum double dose recommended for convalescent serum.

† If exposure continuous repeat serum injection on 10th day.

‡ 4-5 cc. diluent used for each 10 cc. of original serum.

Scarlet Fever Prophylaxis. The value of convalescent scarlet fever serum in passive immunization of exposed individuals is widely recognized. An analysis of many reports, such as that by Hoyne, Levinson, and Thalhimer,⁸ indicates that following the injection of liquid convalescent serum, the case incidence in exposed individuals is approximately 2.5%. The results in this study (Table 2) with vacuum dried serum were essentially the same. There was a case incidence of 2.6% in the group receiving convalescent serum following a more intimate exposure, and a case incidence of 2.2% in the group of 1043 cases receiving convalescent serum.

The symptoms in the majority of the 22 cases developing scarlet fever following the injection of convalescent serum were very mild and there were no complications. It is interesting that 8 of these 22 cases developed the disease between the 11th and 20th days following the administration of serum. Furthermore, all 8 cases remained in the same household with the source of contagion. Previously reported studies¹² on the duration of passive immunity following injection of convalescent serum as shown by the Dick test, would suggest that passive immunity lasts on the average from 10 to 14 days. These earlier studies combined with the clinical studies indicate the advisability of repeating serum injections every 10 days when the exposed individual is to remain in the same household with the source of contagion.

When possible an attempt was made to determine the Dick reaction on exposed individuals prior to serum injection. However, in a disease with such a short incubation period as scarlet fever, parents and physicians are often unwilling to lose the 24 hours which is necessary for the performance of the test. As will be noted in Table 2, 351 of the cases here reported were known to have positive Dick tests prior to the injection of convalescent serum.

In order to determine the value of normal pooled adult serum from Dick negative donors, a series of 152 individuals was given this serum following exposure. Eighty-nine of these contacts were known to be

Dick positive. It would appear from the studies reported that in the absence of convalescent serum, pooled adult serum from immune (Dick negative) donors may be effective in preventing the disease.

The dosage schedule employed for both convalescent and pooled adult serums may be seen in Table 2.

Scarlet Fever Treatment. One hundred and sixty-nine cases of scarlet fever have been treated with vacuum dried convalescent serum. A good response was obtained in 129 (76%) of these cases, which is comparable to the results obtained with liquid serum by Hoyne, Levinson, and Thalhimer⁸ and others. A good response is characterized by a return to a practically normal temperature, a fading rash and absence of or marked diminution in toxemia within 36 to 48 hours following the administration of serum. From 30 to 60 cc. of serum were given at a dose and in the great majority of cases a single dose of serum was sufficient to secure the desired result. Occasionally 2 and even 3 doses of serum are necessary.

The majority of the cases in the early part of this study were injected by the intramuscular route. It is felt, however, that better results are obtained when serum is administered intravenously, and for several years this has been recommended routinely. More rapid absorption and higher concentration result.

The detailed results may be seen in Table 3.

TABLE 3.—SCARLET FEVER TREATMENT WITH CONVALESCENT SCARLET FEVER SERUM (169 CASES)

Result	No. of patients
Good*	129
Moderate†	24
No response‡	16

Dosage: 30 to 120 cc.

Serum given intravenously gives best results.

* Cases whose symptoms subsided in 36 to 48 hours or less. No complications.

† Cases whose symptoms remained longer but showed definite improvement. No complications.

‡ Cases in which serum had no apparent effect, or in which complications developed.

Prophylaxis and Treatment of Whooping Cough. Previous reports on the use of vacuum dried hyperimmune whooping cough serum have been made by McGuinness, Stokes, and Mudd,¹² McGuinness, Bradford, and Armstrong,¹¹ and Katsampes, Bradford, and McGuinness.⁹ This serum is prepared from the blood of individuals who are known to have had pertussis in childhood and who in addition have received repeated injections of pertussis vaccine. The agglutination titer of such serum varies from 1:1280 to 1:5120 with an average of 1:2560 which is of interest in that the agglutination titer of convalescent serum is usually in the range of 1:300. A report on more recent methods of immunization and titration has been made by Flösdorf, McGuinness, Kimball and Armstrong.⁴

The results obtained in passive immunization following exposure and the dosage schedule employed may be seen in Table 4. When the entire group of 215 cases is considered it will be noted that 168 (78%)

failed to contract the disease, 22 (10.3%) developed very mild whooping cough consisting of a mild cough without whooping or vomiting; 12 (5.6%) developed a mild disease in which there was some whooping but no vomiting; and 13 (6%) developed typical whooping cough which was in no instance followed by complications. Particular significance is attached to the group of 106 infants and young children continuously and intimately exposed to siblings with no attempt at isolation. Among this group 71 (67%) failed to develop any symptoms, 16 (15%) developed very mild pertussis, 8 (7.5%) developed mild pertussis, and 11 (10.5%) typical pertussis.

TABLE 4.—WHOOPIING COUGH PROPHYLAXIS HYPERIMMUNE HUMAN SERUM
(215 CASES)

	No disease	Very mild disease*	Mild disease†	Typical disease
Intimate exposure (continuous) 106 cases	71 67%	16 15%	8 7.5%	11 10.5%
Intimate exposure (short duration) 60 cases	50 83.4%	6 10%	3 5%	1 1.6%
Casual exposure (includes ward con- tacts) 49 cases	47 95.8%	0	1 2.1%	1 2.1%
Totals	168 or 78%	22 or 10.3%	12 or 5.6%	13 or 6.1%

* No whooping or vomiting—mild cough of short duration.

† Whooping but no vomiting—short duration.

Dosage of Serum Used:

10–20 cc. depending on age of child and intensity of exposure.‡

A minimum of two 20 cc. injections should be given when exposure continuous.

Serum injection should be repeated in 5 to 7 days.

‡ 4 cc. of diluent used for each 10 cc. of original serum.

The best results appear to be obtained when serum is administered within the first week following the initial exposure.

Vacuum dried hyperimmune serum has been used in the treatment of 315 cases of pertussis following the onset of catarrhal symptoms. Of the 315 cases treated, 123 were infants of 6 months of age and under.

TABLE 5.—WHOOPIING COUGH TREATMENT HYPERIMMUNE HUMAN SERUM
(315 CASES)

Result	No. of patients
Excellent	118
Good	98
Moderate	62
Poor	32
Deaths	5
	(3.2% among 123 infants 6 months of age and under)

Dosage of Serum Used:

20 cc. intramuscularly repeated 3 or 4 times.‡

It may be advisable in critically ill infants to give larger doses intravenously.

* Four deaths in infants under 6 months of age, and 1 death in an 18 month infant. None of these 5 infants received a full course (three or more 20 cc. doses) of serum.

‡ 4 cc. of diluent used for each 10 cc. of original serum.

The results obtained and the suggested dosage schedule may be seen in Table 5. The results are tabulated as excellent, good, moderate,

poor and deaths. An excellent result is one in which virtually all symptoms have disappeared within 1 week of the time serum therapy was instituted. A result is considered good if the major symptoms have disappeared in from 10 to 14 days following the onset of therapy. A moderate result is one in which it can be definitely felt that the symptoms have been lessened by the serum although not in a rapid or spectacular manner.

Four of the 5 deaths which occurred among the 315 treated cases, were in infants 6 months of age or under. Three of these infants were 2 months of age. One died 4 days following the initial dose of serum, having received a total of 40 cc. The second died within 36 hours of the initial dose of serum, having received a total of 40 cc. The third infant died 24 hours after a single 10 cc. dose. All 3 infants were moribund with bronchopneumonia when treatment was first instituted. A fourth infant, age 6 weeks, died 10 days after the initial dose of serum, death being due to an intractable diarrhea. This child likewise received too little serum, having had only two 10-cc. doses, one on the 10th and one on the 5th day prior to death.

One child of 18 months admitted to the hospital in a convulsive state received one 20-cc. dose of serum but died 36 hours after admission.

It appeared necessary to include these cases in this series, although not one had received a full therapeutic course of serum, 3 having died within 36 hours of the initial dose.

In general better results were obtained when treatment was instituted early in the course of the disease. The intravenous administration of 60 to 100 cc. of serum at a dose is now recommended in the case of critically ill infants. It may be desirable to repeat these large doses one or more times.

TABLE 6.—MUMPS PROPHYLAXIS VACUUM DRIED HUMAN SERUM (305 CASES)

	Convalescent serum 200 cases		Pooled adult serum 105 cases	
	No disease	Disease	No disease	Disease
Close exposure	155	18*	38	1
Casual exposure (including hospital)	26	1	60	6†

<i>Dosage Schedule:</i> ‡	Convalescent serum	Pooled adult serum
Age under 5 years	10 cc.§	20 cc.
Age 5 to 12 years	15 cc.	20-30 cc.
Age over 12 years	20-30 cc.	30 cc.

* 15 cases developed a very mild disease; 3 cases developed moderately severe mumps.

† 4 cases developed mumps within 5 days after receiving serum.

‡ If serum is given later than 1 week after initial exposure there can be no assurance of protection or modification.

§ 4-5 cc. diluent used for each 10 cc. of original serum.

Mumps Prophylaxis. Vacuum dried serums have been employed in attempted passive immunization of 305 individuals following exposure to mumps. Two hundred cases received convalescent serum, that is serum obtained during the first 4 months following recovery from the disease; and 105 cases received pooled normal adult serum. The

results obtained and the dosage schedule recommended are shown in Table 6.

It is felt that these results are not as accurate as would be desired inasmuch as many of the individuals treated in this series were adults who may have had mumps during childhood and forgotten they had had the disease. However, the series includes a sufficient number of presumably susceptible children who have received serum following close exposure and the data indicate that convalescent serum is probably effective to a certain degree. Its use appears to be justified in the absence of more specific measures. The results presented here are comparable to reports by Hess,⁷ Barenberg and Ostroff,¹ and others; but well controlled studies with either vacuum dried or liquid serum have not been carried out.

It is possible that in the absence of convalescent serum, pooled normal adult serum may have some degree of effectiveness in passive immunization against mumps.

TABLE 7.—CHICKENPOX PROPHYLAXIS VACUUM DRIED HUMAN SERUM (239 CASES)

	Convalescent serum 59 cases		Pooled adult serum 180 cases	
	No disease	Disease	No disease	Disease
Home	6	10	23	5
Hospital	42	1	131	21

Dosage Schedule:*	Convalescent serum	Pooled adult serum
Age under 6 years	10-15 cc.†	20 cc.
Age over 6 years	20 cc.	30 cc.
Age 12 years and over	25-30 cc.	30 cc.

* If serum is given later than 1 week after initial exposure there can be no assurance of protection or modification.

† 4-5 cc. diluent used for each 10 cc. of original serum.

Chickenpox. Vacuum dried convalescent and normal pooled adult serums have been employed in the attempted passive immunization of 239 individuals following exposure to chickenpox. The results obtained and the dosage schedule employed may be seen in Table 7. Passive immunization against chickenpox was relatively unsuccessful. Attempts to prevent the spread of the disease on hospital wards with pooled normal adult serum have, with a few exceptions, failed. A number of the cases of chickenpox developing after the injection of convalescent serum have been mild, but more individuals developed the disease than were protected. These results do not agree with those reported by Gordon and Meader⁵ and others who employed liquid convalescent serum. But, as in the case of mumps prophylaxis, well-controlled studies are not yet available for comparison.

On the whole, it would seem that attempted passive immunization against chickenpox with convalescent or pooled normal adult serums is only justified when there are special indications to prevent the development of the disease.

Reactions. In general, reactions following the intramuscular injection of vacuum dried serums are negligible. Local discomfort at the

site of injection generally lasts for from 12 to 24 hours, particularly in older individuals. A few individuals have a slight temperature rise of $\frac{1}{2}$ to 1° F., lasting for 12 to 24 hours. On rare occasions a temperature elevation to 102° F. or 103° F. results. Several cases of delayed serum sickness have been encountered, but the incidence was less than 0.1% of individuals receiving human serum. No acute anaphylactic reactions have occurred following the intramuscular injection of vacuum dried serums.

In the early years of this study a number of sharp febrile and shock-like reactions occurred following the intravenous injection of these serums. It is now felt that these reactions were probably due to early faulty technique in handling the serums prior to vacuum dehydration, for in recent years vacuum dried serums have been given intravenously with no greater occurrence of reactions than with serums prepared and preserved in the liquid state.

Summary. Human serums dried *in vacuo* from the frozen state have been employed in passive immunization against measles, scarlet fever, whooping cough, mumps, and chickenpox, and in the treatment of scarlet fever and whooping cough.

With the exception of chickenpox, in which both convalescent and pooled adult serums frequently failed to protect, satisfactory results have been obtained. The results in mumps prophylaxis are not conclusive, but strongly suggest that serum may be of value.

Particular interest has been focused on the value of pooled normal adult serum in passive immunization against measles, and on the use of "hyperimmune" whooping cough serum in the prevention and treatment of that disease.

It would appear from these studies that serums dried *in vacuo* from the frozen state may be given either intramuscularly or intravenously with no more reaction than from injection of the same materials preserved in the liquid state; and the clinical results are comparable to those reported by other investigators who have employed similar serums preserved in liquid form.

Vacuum dried serums may be stored over long periods of time without deterioration and may be redissolved in a small fraction of their original water content, thus permitting concentration prior to injection.

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TOXIC EFFECTS OF PROMIN (SODIUM P,P'-DIAMINODIPHENYL-SULFONE-N,N'-DIDEXTROSE SULFONATE) ON THE ERYTHROCYTES OF GUINEA PIGS

BY GEORGE M. HIGGINS, PH.D.

ROCHESTER, MINN.

(From the Division of Experimental Medicine, Mayo Foundation)

IN a series of well-controlled experiments Feldman, Hinshaw and Moses⁴⁻⁶ have shown that promin is an effective therapeutic agent for the control and the cure of experimental tuberculosis in guinea pigs. Promin has also been used successfully to combat infections which were induced by hemolytic streptococci,¹⁹ by pneumonococci⁷ or by gonococci.¹³

Following these initial studies on the course of tuberculosis in experimental animals, Hall and his colleagues¹⁰ presented a preliminary report on the data assembled from the blood of patients who had received promin for clinical tuberculosis. These authors confirmed the observation that promin is toxic and showed that the drug caused excessive destruction of the blood, resulting in anemia apparently hemolytic in type.

My interest in these studies on promin evolved from the tentative observation of Feldman that the drug induced anemia in his tuberculous animals. Interested in experimental anemia, I undertook to study the peripheral blood and the hemopoietic organs of normal guinea pigs which were given promin by mouth. Adequate amounts of promin were provided by Dr. E. A. Sharp of Parke, Davis Company and I wish to acknowledge indebtedness to him for his courtesy and interest in this study. This report is restricted to the data assembled from my study of the erythrocytes of these animals.

Methods of Study. Twenty guinea pigs, free from any external evidence of disease and having an average body weight of 317.4 gm., were selected from our stock colony. They were arranged into 4 groups of 5 animals each, housed in metal cages, 2 animals to a cage, and fed our standard ration. One group received 100 mg. of promin daily; a second group, 200 mg. daily; a third group, 300 mg. daily, and a fourth group, water only as controls.

As our study was of short duration, we provided each guinea pig its daily allotment of promin by means of a calibrated pipet inserted into the mouth, instead of adding the drug directly to the diet in a 1% concentration (300 and 400 mg. of promin each day), as in Feldman's study. Promin was given for 21 days in the amounts indicated. It was then withdrawn and the animals were followed for 21 days more, recovery from the toxic effects being observed.

All examinations of blood were made on a single sample withdrawn from the heart with a 2 cc. Luer syringe, equipped with a 23-gauge needle. This

sample was transferred to a chemically clean glass slide and all determinations made from the single sample. The number of erythrocytes per c.mm. was determined in pipets approved by the U. S. Bureau of Standards, using the Bright-Line Improved Neubauer counting chamber. Hematocrit determinations were made with the Van Allen tubes; erythrocyte volumes (in c. μ) from the hematocrit reading and the total erythrocyte count; the amount of hemoglobin (gm. per 100 cc.) by means of the Cenco-Sheard-Sanford photometer. Two slides were prepared of each sample of blood obtained; one was stained with brilliant cresyl blue counterstained with Wright's stain, for study of the reticulocytes; and the other was stained with the May-Grünwald Giemsa technic.

Results. The daily administration of promin in the amounts stated was apparently without deleterious effect on the general appearance of these guinea pigs during the first week. All increased in weight and their intake of food was satisfactory. During the second week some changes were observed. Loss of appetite and weight was experienced by some animals, so that by the end of the second week 1 animal which had received 200 mg. daily and 2 which had received 300 mg. daily were dead. During the third week the same number of deaths occurred, so that at the end of the third week, when the drug was withdrawn from all animals, there were 14 animals: 5 controls, 5 which had received 100 mg. daily, 3 which had received 200 mg. daily, and 1 which had received 300 mg. daily still alive.

Toxic effects, certainly not evident grossly at the end of the first week, were definitely demonstrated in the samples of blood taken at that time. The effects were most marked in animals which had received the larger amounts of the drug. Cardiac blood was dark in all the experimental animals; but in those receiving 200 and 300 mg. daily, it was thin and of a deep chocolate color. Spectrophotometric examination (by Dr. Charles Sheard) of oxalated samples of blood showed the presence of sulfhemoglobin in some animals and methemoglobin in others. A number of blood samples included an intermediate, as yet undetermined, product which had an absorption band of 626 to 628 m. μ . These pigments were not in the plasma, but in the erythrocytes, for centrifuged samples contained a clear supernatant plasma, but dark, almost black, packed erythrocytes. These pigments are the result of some chemical changes in the hemoglobin induced by promin after its passage through the gastro-intestinal mucosa; for we have not seen such color changes as yet when the drug was given intravenously.

TABLE 1.—ERYTHROCYTE DATA ASSEMBLED AFTER 1 WEEK OF ADMINISTRATION OF PROMIN

(The figures in parentheses indicate ranges observed)

Amount of drug daily mg.	No. of animals	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
None	5	5.41 \pm 0.08 (5.20 - 5.95)	82.7 \pm 1.1 (80.0 - 87.0)	12.7 \pm 0.3 (11.2 - 13.6)	1.2 \pm 0.2 (0.6 - 2.5)
100	5	4.40 \pm 0.06 (4.05 - 4.60)	88.6 \pm 1.4 (84.4 - 96.5)	10.5 \pm 0.3 (9.1 - 11.2)	7.8 \pm 0.6 (4.8 - 11.2)
200	5	3.56 \pm 0.20 (2.90 - 4.45)	116.5 \pm 3.2 (98.9 - 130.0)	10.5 \pm 0.5 (8.8 - 12.0)	5.2 \pm 0.9 (2.3 - 8.9)
300	5	3.54 \pm 0.20 (3.05 - 4.35)	111.1 \pm 3.9 (92.0 - 125.7)	9.3 \pm 0.2 (8.5 - 9.8)	11.8 \pm 2.3 (3.0 - 24.0)

All data on the toxic effect of promin on the erythrocytes assembled at the end of the first week were condensed into Table 1. Average determinations, together with their standard errors, are given, and the range or spread of the data is also included. Data assembled from the 5 control animals were not altered significantly from those obtained from the 20, prior to giving promin (Table 2). But animals which had received 100 mg. of the drug each day now showed a significant decline of their total erythrocyte counts and of concentration of hemoglobin, together with an increase of cell volumes and of reticulocyte percentages.

TABLE 2.—CONTROL DATA BEFORE ADMINISTRATION OF PROMIN

No. of animals	Sex	Body wt., gm.	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
20	M	317.4 (280-352)	5.40 \pm 0.07 (4.75 - 6.10)	82.1 \pm 1.8 (75.4 - 90.5)	13.0 \pm 0.09 (11.6 - 14.6)	1.8 \pm 0.2 (0.7 - 3.9)

All animals did not respond alike to comparable amounts of promin. Of the 5 which received 200 mg. daily, 1 at the end of the first week had an erythrocyte count of 2,900,000 in each c.mm. of blood, while a mate had a count of 4,450,000, which was close to the lower limit of the normal range. Regenerative capacities, indicated by cell volumes and reticulocyte percentages, were most marked in animals which had sustained the greatest toxic damage.

Whereas the distribution induced in animals by the daily doses of 200 mg. was significantly different from that of those given 100 mg., there were no essential differences between the data derived from the 200 mg. and 300 mg. groups. The addition of 100 more mg. did not appear to inflict any more damage on the red cells than did 200 mg. of drug. The degree of anemia, the extent of the macrocytosis and the hemoglobin levels were statistically alike in the 2 groups at the end of the first week. There was, however, a significant difference in their reticulocyte percentages. This is due to the fact that 1 animal, which had an erythrocyte level of 3,000,000 in each c.mm., had the unusually high reticulocyte level of 24%.

At the end of the second week the degree of anemia was greater than before in animals which had received the daily doses of 100 mg. The mean number of erythrocytes had dropped to 4,080,000, and their size had increased to a mean of 105.7 c. μ . Hemoglobin levels and reticulocyte percentages remained unchanged. But in both groups which received the larger amounts of the drug, increased toxic changes, greater than those recorded at the end of the first week, were not observed at the conclusion of either the second week or the third week of administration of promin. The animals appeared to acquire a tolerance for the drug and manifested a blood regenerative capacity which maintained the levels of erythrocytes and hemoglobin at a satisfactory minimum. Elevated percentages of reticulocytes were proof that the bone marrow had not been injured seriously by the drug.

In Figures 1, 2, 3 and 4, stained smears show the appearance of the erythrocytes in the blood of a normal animal and of animals at the end of the third week of administration of promin. Reticulocytosis,

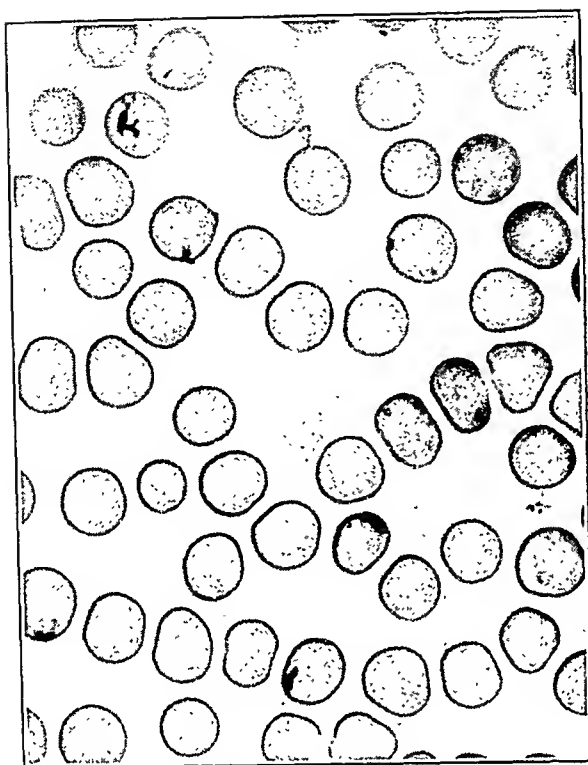


FIG. 1.—Blood smear of a normal guinea pig.



FIG. 2.—Blood smear of guinea pig after receiving 100 mg. of promin daily for 3 weeks. Polychromatophilia, regeneration and crenation are shown.

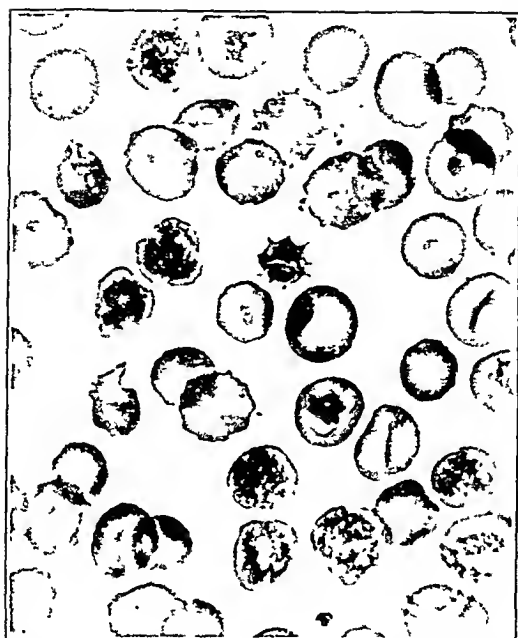


FIG. 3.—Blood smear of guinea pig after receiving 100 mg. of promin daily for 3 weeks. Reticulocytes are shown, but they are not crenated.



FIG. 4.—Blood smear of guinea pig after receiving 200 mg. of promin daily for 3 weeks. Most of the erythrocytes in the circulating blood are crenated.

macrocytosis, hyperchromatophilia and crenation of the mature erythrocytes have occurred.

To determine the irreversibility of these changes induced in the erythrocytes by promin, we withdrew the drug from all animals but continued to observe the blood at weekly intervals for 3 weeks thereafter. Elevated erythrocyte counts, reduced erythrocyte volumes and increased hemoglobin levels occurred immediately. The data, assembled after the third week of recovery, from the 14 surviving animals is presented in Table 3, showing that promin had not induced any permanent damage to the hemopoietic system.

TABLE 3.—DATA ASSEMBLED 3 WEEKS AFTER DISCONTINUING ADMINISTRATION OF PROMIN

Amount of drug daily mg.	No. of animals	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
None	5	5.77 \pm 0.15 (5.35 - 6.76)	81.7 \pm 2.05 (70.0 - 88.0)	13.9 \pm 0.31 (13.2 - 15.3)	1.14 \pm 0.15 (0.6 - 2.0)
100	5	4.87 \pm 0.12 (4.30 - 5.48)	91.8 \pm 2.88 (80.3 - 106.9)	12.7 \pm 0.22 (12.4 - 13.0)	1.7 \pm 0.28 (0.8 - 3.1)
200	3	4.55 \pm 0.12 (4.20 - 4.95)	99.8 \pm 3.56 (90.9 - 111.1)	12.3 \pm 0.47 (11.2 - 13.0)	1.2 \pm 0.29 (0.5 - 2.3)
300	1	4.90	95.9	12.4	1.4

Comment. Changes which were induced in the blood of the guinea pigs by promin resembled qualitatively those hitherto described following the administration of sulfanilamide, other sulfonamides¹⁴⁻¹⁸ and drugs.^{1,2,9,11} They conform in general to those which occurred following the administration of the drug to tuberculous patients. Feldman, Hinshaw and Moses⁶ gave 300 to 400 mg. daily in their diets to guinea pigs weighing 500 gm. Therefore their doses ranged from 600 to 800 mg. daily per kilogram of animal weight. The average weight of our guinea pigs was 317.4 gm., so that our doses ranged from 310 mg. per kilogram of body weight in the group which received 100 mg. daily to 930 mg. per kilogram of body weight in the group which received 300 mg. daily.

The effect of the drug is apparently directly on the erythrocyte and the anemia which ensued is the result of chemical and physical changes in the erythrocytes (Fig. 4), their destruction, and their final removal from the blood stream, largely by the spleen. Accompanying these changes, pigments were formed in the cells, so that samples of blood drawn a week after administration of promin was started were very dark and showed by spectrophotometric analysis the presence of sulfhemoglobin, methemoglobin and in certain animals an additional product as yet undetermined, but having its own characteristic absorption band.

Crenation of erythrocytes, observed in "cover slip" preparations of the blood of animals given promin, will occur equally well in *in vitro* preparations. When varying concentrations of promin were added to oxalated preparations of whole blood, crenation occurred immediately, and in fresh "cover slip" preparations the proportion of such crenated cells was found to correlate with the amount of promin added to a given sample of blood. Crenated cells, however, were not identified

in "cover slip" preparations made of heart blood taken from an animal which had received the drug by way of the saphenous vein. It is likely that following an intravenous injection the protective organs, liver, spleen and bone marrow, readily remove all damaged cells from the circulation. But the slow absorption from the gastro-intestinal tract of the orally administered drug resulted in a continuous action so that damaged erythrocytes were encountered more readily. These changes are somewhat like those hitherto described, when erythrocytes are subjected to other substances which set up changes of permeability and osmotic pressure, and perhaps in the cell membrane itself.^{3,9}

The blood picture in these animals is, in some respects, like that of clinical hemolytic anemia.⁸ Typical spherocytosis of the erythrocytes, such as found in familial hemolytic (spherocytic) anemia, however, was not observed in these bloods. Other symptoms of hemolytic anemia, such as increased pigment content of the bile and of the urine, elevated percentages of reticulocytes and greatly enlarged spleens, were observed in these animals.

In clinical hemolytic anemia, erythrocytes begin to hemolyze at higher concentrations of solutions of sodium chloride than do normal erythrocytes. In other words, they are more fragile and less resistant to hypotonic solutions. In normal guinea pigs, Musser and Krumhaar¹⁶ showed that hemolysis began at 0.42% of sodium chloride and was complete at 0.31% of sodium chloride. More recently Kato¹² stated that hemolysis began at 0.45% and was complete at 0.33%. Our data show the range to be from 0.44% to 0.30%. Blood samples, taken from animals which had had promin daily for 2 weeks, showed an increased resistance in that beginning hemolysis occurred at 0.40% sodium chloride concentration, and complete hemolysis at 0.20% concentration.

Summary and Conclusions. A study of the effects of promin (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate), when given orally to guinea pigs, on erythrocytes is reported. Five guinea pigs were given 100 mg. daily; five, 200 mg.; five, 300 mg.; and five served as controls. The following conclusions were drawn from the study:

1. Promin is a toxic drug and in large amounts may kill an animal. At the end of 3 weeks of daily administration, 2 animals were dead in the group which received 200 mg. daily, and 4 were dead in the group which received 300 mg. daily.

2. Promin exerts a direct toxic effect on the erythrocytes, manifested by the presence of abnormal hemoglobin pigments in the cells and by changes in the surface membranes, so that in fresh "cover slip" preparations many cells are crenated.

3. Damaged erythrocytes are removed from the blood stream by the spleen. Anemia is induced, the spleens are greatly enlarged and percentages of reticulocytes are elevated.

4. The anemia is a hemolytic anemia, although some of the features of familial hemolytic (spherocytic anemia) were not present. The erythrocyte volume was increased, spherocytosis was absent, and resistance to hypotonic salt solution was increased.

5. The blood and the spleens were excessively dark. Spectrophotometric analysis showed the presence in the erythrocytes of sulfhemoglobin, methemoglobin and an additional unidentified pigment which had an absorption band intermediate between those of sulfhemoglobin and methemoglobin.

6. Promin did not induce any permanent damage of the bone marrow. Regeneration of erythrocytes, indicated by reticulocytosis, macrocytosis and polychromatophilia, proceeded in the face of continuous administration of large amounts of the drug.

7. Morphologic changes, induced in erythrocytes *in vivo* by promin, may be observed in *in vitro* preparations as well.

8. Although the drug is toxic, no permanent damage to any part of the organism was observed when sublethal doses were given.

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FEBRILE REACTIONS RESULTING FROM THE READMINISTRATION OF SULFADIAZINE*

By TIMOTHY R. TALBOT, JR.

LIEUTENANT (J.G.), M.C., U.S.N.R.

AND

JOHN D. ADCOCK, M.D.

ASSISTANT PROFESSOR OF INTERNAL MEDICINE, UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL, ANN ARBOR, MICHIGAN

(From the Pennsylvania Hospital, Philadelphia, Pa.)

It has become an accepted fact that unfavorable reactions occur less frequently in patients treated with sulfadiazine than in patients to

* These studies were undertaken when both authors were members of the staff of the Pennsylvania Hospital.

whom sulfanilamide, sulfapyridine or sulfathiazole has been given.^{1,12,18} It has also been established, however, that the use of sulfadiazine is not without danger, and that undesirable reactions may result from its use.^{1,3,6,7,8,11,12,13,14,19,20,24} Several investigators have reported acquired sensitivity to the sulfonamide drugs.^{4,10,12,17,21,22,23,24,25} The term "acquired sensitivity," as used here, is intended to imply a sensitivity resulting from either (a) prolonged continuous administration of one of the sulfonamide drugs, or (b) readministration of the same drug after an interval of time has elapsed. Lyons and Balberor¹⁵ state that the administration of a second course of sulfathiazole resulted in a febrile reaction in 36% of their cases, whereas in those patients who received the drug in one continuous course which lasted for 7 or more days, the incidence of fever was 10.4%. They also state that no febrile reaction was seen in patients prior to the 9th day after the initial exposure to the drug.

The observation of several patients who exhibited unfavorable reactions to sulfadiazine led us to make the following survey. In order that our data on sulfadiazine might be compared with the published data on sulfathiazole, we have in most respects followed the methods of Lyons and Balberor.¹⁵

TABLE 1.—CONDITIONS FOR WHICH SULFADIAZINE WAS ADMINISTERED THERAPEUTICALLY

Condition	No. of patients
Lobar pneumonia	7
Empyema thoracis	1
Bronchopneumonia	1
Lung abscess	2
Pneumonia due to <i>B. aerogenes</i>	1
Virus pneumonia	1
Isohiorectal abscess	1
Cystitis	1
Stab wound of chest	1
Infected index finger	1
Ulcerative colitis	1
Superficial infection of abdominal wound	1
Chronic infection involving chest wall	1
Total	20

Material. Thirty-seven patients who had received one course of sulfadiazine were given a second course. Of these, 20 had received the first course for therapeutic purposes (Table 1), and 17 patients were given a first course of sulfadiazine for experimental purposes. The reasons for hospitalization of the latter group are listed in Table 2.

Dosages. The dose of sulfadiazine used therapeutically in the group of 20 patients varied in the initial amount from 2 to 4 gm., followed by 1 gm. every 4 to 6 hours throughout the first course. Each patient in the experimental group received an initial dose of 4 gm., followed by 1 gm. every 4 hours for 6 doses, then by 1 gm. every 6 hours for 8 doses, or a total of 18 gm. The amount of the drug used in the second course was the same for all patients as the first course given to the experimental group, except in those cases exhibiting a reaction.

The mean duration of the first course in all patients was 6.97 days, with a variation of from 2 to 30 days. The second course was started in from 8 to 50 days (mean time 15.4 days) after the completion of the first course. No patient in the series had shown evidence of fever for at least 5 days prior to the commencement of the second course.

TABLE 2.—CONDITIONS AFFECTING THOSE PATIENTS WHO RECEIVED SULFADIAZINE FOR EXPERIMENTAL PURPOSES

Condition	No. of patients
Syphilitic heart disease	2
Myocardial infarction	2
Arteriosclerotic heart disease	1
Hypertensive heart disease	1
Cerebral hemorrhage	1
"Saturday night palsy"	1
Dermatomyositis	1
Minimal pulmonary tuberculosis	4
Gastric ulcer	1
Gastric hyperacidity	1
Eczema	1
Diagnosis not established	1
Total	17

TABLE 3.—PATIENTS WHO REACTED TO THE SECOND COURSE OF SULFADIAZINE

Case	Reason for 1st course	Duration 1st course (days)	Interval between courses (days)	Max. temp. (° F.)	Chill	Rash	Psychosis	Total white count during reaction	Remarks
H. G.	Cystitis	10	12	100.4	+++	+	+++	10,600	Toxic psychosis for 12 hrs.
R. S.	Virus pneumonia	8	16	100.0	0	0	++	Not done	Severe delirium for 3 to 4 hrs.
L. A.	Experimental	3	28	100.0	Sl.	0	0	Not done	Slight malaise
L. C.	Infected finger	10	11	99.8 102.0 100.0	0 0 0	++ + 0	0 0 0	Not done 4,900 Not done	Reacted to: 1st course, 2d course of 2 gm., 3d course of 0.25 gm.,
N. S.	Ischiorectal abscess	18	20	102.8 101.4 101.2	+++ ++ +	+++ + 0	+++ ++ +	5,850 6,000	Delirium for 4 to 6 hrs., reacted to: 1st course, 2d course of 2 gm., 3d course of 1 gm.
R. L.	Ulcerative colitis	10	17	100.0 101.0	0 0	+ 0	0 0	9,000 Not done	Delirium for 4 to 6 hrs., reacted to: 1st course, 2d course, did not react to 2 gm. of sulfanilamide or sulfapyridine

Studies. Blood sulfadiazine levels were determined on the 2d or 3d days of both courses in most patients, and were consistently between 6 and 14 mg. per 100 cc. If the duration of the treatment was longer than 4 days the determination was often repeated. Blood counts (hemoglobin and total white count) were taken on every patient before and after each course, and a differential count was done in most cases that showed a reaction of any type. The differential distribution was never altered from the normal, and the total white counts were not remarkable, as may be seen in Table 3. The urine of every patient was examined at regular intervals, and nothing untoward was discovered in routine studies (*i. e.*, no red cells, casts or albumin). Crystals of sulfadiazine were not infrequently seen in the urine specimens, but no attempt was made to correlate their presence or absence with the occurrence of a febrile reaction.

Criterion for Reaction to the Drug. Our arbitrary criterion for a significant reaction to sulfadiazine was a fever of at least 100° F. which could not be explained on the basis of any other mechanism.

The most frequent manifestations of a reaction were, in addition to fever, chills or a sensation of chilliness, diffuse skin eruptions, severe malaise, and toxic psychoses. These signs and symptoms all appeared, as a rule, within a few hours after the onset of the second course, and always appeared within 24 hours of that time. The administration of the drug was stopped as soon as fever became manifest or when any other evidence heralded a reaction.

Results. Of 37 patients who were given a second course of sulfadiazine, 6 (16.2%) had fever during the second course, 3 (8.1%) reacted to both the first and second courses, and 3 (8.1%) reacted to only the second course. Four had a diffuse maculopapular eruption, and all had either frank chills or chilly sensations.

A third course was given to 2 of the patients (L. C. and N. S., Table 3) who had reacted to the second course. The reaction was reproduced with each course.

One patient (R. L., Table 3) who reacted to the first course had received sulfathiazole immediately prior to the sulfadiazine, and he reacted to the latter on the 9th day of its administration. He subsequently failed to react to sulfapyridine, or sulfanilamide, but did respond again to sulfadiazine. Another patient (N. S.) had fever, rash, and delirium 3 days after the cessation of the first course, 21 days after its beginning. He subsequently reacted to a second and third course. Four patients (R. L., R. S., N. S. and H. G.) had delirium which was far out of proportion to the amount of fever.

Once a reaction had occurred the fever persisted for periods which varied from 12 to 48 hours.

Comment. It is well known that toxic reactions to the sulfonamides are most likely to occur in those cases to whom the drug has been administered continuously for periods of 9 or more days, or to whom the drug is readministered after an interval of several days.¹²

In order to determine with the greatest significance the effects of readministration, one would wish to know the incidence of reactions in the aggregate of the patients who received the drug for at least 9 or more days. The incidence of fever in response to sulfadiazine therapy is reported as 3%,^{5,13} 1%,¹² as apparently very rare;¹⁰ 1.6%,⁶ 0.2%,⁸ and 0.5%;⁹ or an average of about 1.5%. One may assume that most of these cases received the drug for less than 1 week, and can only reiterate the statement that the less prolonged courses are less likely to yield reactions.

In our series, 10 cases received a first course of sulfadiazine which was 10 or more days in length, and 3 (30%) had a reaction to the first course. The mean length of the first course in these patients was 14.2 days, with extremes of 10 and 30 days. Two of the 3 patients who reacted to only the second course had received a first course which was longer than 8 days. These facts are admittedly not of sufficient scope for significant statistical analysis, although they prompt the suggestion that febrile reactions are more likely to occur in patients receiving prolonged courses of sulfadiazine than is at present appreciated.

Lyons and Balberor noted a much higher incidence of febrile reac-

tions to the readministration of sulfathiazole than to the administration of the first course. They attributed this increase to the development of hypersensitivity to the drug during the interval. The same thing is true, but to a lesser degree, in our series of sulfadiazine readministration, particularly among those patients who received the drug initially for short periods. We do not feel that there is sufficient evidence, however, that the development of sensitization is enhanced by an interval between courses in contrast to the continuous prolonged administration of the sulfadiazine. We have nothing new to add to the theories of the mechanism of the reactions to sulfonamides which have been discussed in recent publications.^{2,16,25}

This study indicates that reactions to sulfadiazine are less severe than those reported for sulfathiazole. One feature of the reactions to sulfadiazine which was of particular interest was the occurrence of severe delirium in 4 cases. It usually lasted only a few hours but was out of all proportion to the amount of fever present. We cannot be certain that these febrile reactions are, in themselves, productive of permanent injury. Nevertheless, it is clear that until evidence is presented which shows definitely that they are not harmful, this drug, as well as other sulfonamide compounds, should be used with increasing discretion and caution.

Summary. 1. Six of 37 patients (16.2%) experienced a febrile reaction to sulfadiazine. Three (8.1%) experienced a febrile reaction to both the first and second courses and 3 (8.1%) to the second course.

2. Febrile reactions to a second administration of sulfadiazine are less frequent and less severe than those reported for sulfathiazole.

3. Febrile reactions to the readministration of sulfadiazine are frequently accompanied by delirium, chill, and a maculopapular rash.

4. Sulfadiazine, as well as the other commonly used sulfonamides, should be given only in those cases which with certainty justify its administration, although no evidence is presented to show that the febrile response *per se* is harmful.

We wish to express our thanks to Miss Harriett Hosmer, R.N., for her willing and careful assistance with this work; and to Dr. L. S. Carey, Dr. John B. Flick and Dr. Walter E. Lee, for their permission to study patients who were on their services at the Pennsylvania Hospital.

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STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERAZINE, SULFAMETHYLDIAZINE) IN MAN*

II. TOXIC MANIFESTATIONS

BY JOHN K. CLARK, M.D.

EDWARD BOK FELLOW IN MEDICINE

HARRISON F. FLIPPIN, M.D.

ASSOCIATE IN MEDICINE

AND

FRANKLIN D. MURPHY, M.D.

GODEY AND SEEGER FELLOW IN MEDICINE
PHILADELPHIA, PA.

(From the Department of Medicine and the Hospital of the University of Pennsylvania)

In a recent paper³ we reviewed the experimental data pertaining to the therapeutic activity, pharmacologic behavior, and toxicity of sulfamerazine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine), and presented observations on the absorption, distribution, and excretion of the drug in man. The purpose of this communication is to discuss certain toxic effects which have been encountered following the clinical use of sulfamerazine† in the treatment of several types of infection.

Clinical Material and Methods. Included in this study are the first 200 unselected patients‡ who were treated with sulfamerazine for at least 4 days, or received no less than 10 gm. of the drug. For the most part they included adult patients suffering with acute infection, such as pneumococcal pneumonia, the bacterial meningitides, gonococcal urethritis, and non-specific urinary tract infections. In general, the drug was given orally, with an initial dose of 3 gm., followed by 1 gm. every 6 to 8 hours until the temperature had remained normal for 48 to 72 hours. In severe infections, such as meningitis, the initial

* This work was aided by a grant from the Sharp & Dohme Laboratories, Glenolden, Pa.

† Sharp & Dohme Laboratories, Glenolden, Pa., kindly supplied the sulfamerazine used in this study.

‡ These cases were treated at the Hospitals of the University of Pennsylvania and the Philadelphia General Hospital and will be included in future reports dealing with the therapeutic effectiveness of sulfamerazine.

dose of 3 gm. was usually administered by vein (sulfamerazine sodium) and followed by 1 gm. by mouth every 4 hours. Patients with urinary tract infections received 2 gm. of the drug daily at 12 hour intervals in equally divided doses. The range of dosage in the entire series was from 10 to 114 gm., given over periods varying from 4 to 24 days. With the exception of 10 cases of gonococcal urethritis, all of the patients were hospitalized and were closely followed with appropriate laboratory studies. Fluids were given liberally, usually from 2000 to 3000 cc. a day, but none of the patients received alkalies.

Toxic Manifestations. A summary of the various toxic manifestations encountered in 200 patients receiving sulfamerazine is given in Table 1. Toxic reactions, attributable to the drug, excluding simple crystalluria, were noted in 30 patients (15%).

TABLE 1.—SUMMARY OF TOXIC MANIFESTATIONS OCCURRING DURING TREATMENT WITH SULFAMERAZINE (200 CASES)

Toxic effect	No. of cases	%
Hematuria:*		
Microscopic	16	10 0
Gross	2 (1)†	1.3
Acute loin pain	1	0 5
Nausea and vomiting	8 (1)†	4 0
Rash	6	3 0
Fever	5	2 5
Leukopenia	4 (1)†	2 0
Thrombocytopenia	1†	0 5
Psychosis	2	1 0

* On the basis of 160 cases (40 urologic patients were excluded).

† Massive dosage (Table 3).

Urinary Tract Complications. Clinical experience with the sulfonamides, excepting sulfanilamide, has shown that the toxic effects involving the urinary tract, namely hematuria, suppression of urinary output and renal colic, represent the most significant untoward manifestations. These complications are related to solubility of the drugs, especially the acetyl derivatives. Because of the relatively greater solubility of both sulfamerazine and acetylsulfamerazine in urine,⁴ as compared to the sulfonamides now in common use, one might expect to encounter less urinary tract toxicity with this compound. In this series of cases crystalluria was observed in 36 patients (18%); but we have not considered the presence of crystalluria as evidence of urinary tract involvement unless it was associated with other urinary complications. No doubt additional cases of crystalluria would have been detected if every specimen of urine voided during each 24 hour period had been examined.

Microscopic hematuria, as evidenced by the finding of red blood cells in a single specimen, was encountered in 10% of the patients. Although we have attributed this urinary abnormality to sulfamerazine, it should be stressed that in many instances the patient's disease might well explain these findings when one considers the type of infections under treatment. Four of the cases in this sub-group showed occasional crystals of the drug in the urine.

Gross hematuria was observed in 2 patients; and in 1 of these acute loin pain was also present. Because of the importance of these un-

toward reactions, a few remarks concerning the salient features of both cases are worthy of special comment.

Case Studies. CASE 1 (Table 2). A. W., a white woman, aged 18, was treated in a routine manner with sulfamerazine for meningococcal meningitis. The patient responded well to chemotherapy and her illness was uneventful until the 14th day of treatment, at which time she suddenly experienced a sharp pain in the right loin region. Following this attack, which lasted approximately 20 minutes, the patient was catheterized and a sample of urine from the bladder contained many crystals of the drug and innumerable red blood cells. At no time after the attack did the patient offer any symptoms or laboratory evidence of any urinary tract disturbance. As indicated, the urinary output was 1300 cc., or better, for the 24 hour periods preceding, the day of, and following the apparent ureteral blockage. The serum drug levels, taken several hours before the attack, were not excessive and, although the degree of acetylation was higher than is usually seen with sulfamerazine,³ it was in keeping with previous readings in this case. A total of 77 gm. of the drug had been given before the onset of the urinary toxic reaction, after which the drug was discontinued.

TABLE 2.—ACUTE LOIN PAIN AND GROSS HEMATURIA

CASE 1. A. W., a white woman, aged 18. Type I meningococcal meningitis with bacteremia successfully treated with sulfamerazine

Day	Dose (gm)	Serum sulfamerazine				Urine					Blood				Comments
		Free (mg /100 cc)	Total (mg /100 cc)	Acetylated (%)	Fluid intake (cc)	Output (cc)	Specific gravity	Reaction	Crystals	R B C	Hemoglobin (%)	Leukocytes per c mm.	Neutrophils per c mm	Urea nitrogen (mg /100 cc)	
1	3*				1500	900+	1.027	Acid	0	0	92	15,500	12,400	32	Vomiting on admission
2	6*	10.8	13.7	21	3550	?									Vomiting
3	6*	10.5	13.4	22	1930	600+			0	0	81			21	
4	6	10.0	16.2	38	1400	?			0	0	77	15,100	13,000		
5	6	8.5	14.3	40	2300	?			0	0	81				
6	6	6.5	10.7	39	2945	?									
7	6	5.2	6.7	22	2265	?	1.030	Acid	0	0	79				
8	6	6.4	8.2	22	2840	?					79				
9	6	7.3	9.1	19	1760	450+	1.020	Acid	0	0	63				
10	6	7.4	9.4	21	2220	800+					84	9,800			
11	6	9.6	14.0	32	2310	1350+					76	8,000			
12	6	8.5	12.5	32	2500	800+									
13	6	12.0	15.8	24	2600	1300+	1.020	Acid	+	0					
14	2	9.9	13.4	36	3500	1350+			++++	Gross					
15		1.9			3750	1850+	1.020	Acid	+	0	70	6,800		6	Acute loin pain
16		0.1			3000	1400+	1.015	Acid	0	0				6	Symptom-free
17					2550	1350+									
18											70	6,200		8	

* Intravenous administration (5% sulfamerazine sodium).

CASE 2 (Table 3). R. S., a white male, aged 30, was given a massive dose of sulfamerazine for subacute bacterial endocarditis. During the first 3 days of chemotherapy the patient received a total of 14 gm. of the drug with no apparent untoward effect. On the morning of the 4th day he was given 25 gm. (sulfamerazine sodium) by vein over a 30 minute period. A free drug level taken 1 hour after the infusion was 106 mg. per 100 cc. of serum. The first

Day	Dose (gm.)	Serum			Urine			Urine			Blood			Comments						
		Free (mg./100 cc.)	Total (mg./100 cc.)	Acetylated (%)	Free (mg./100 cc.)	Total (mg./100 cc.)	Acetylated (%)	Daily excretion (gm.)	Fluid intake (cc.)	Output (cc.)	Specific Gravity	Reaction	Cystals		R.B.C.	Hemoglobin (%)	Leucocytes per c.mm.	Neutrophils per c.mm.	Platelets per c.mm.	Urea nitrogen (mg./100 cc.)
1	2	22.8	24.6	7.3						550	1.017	Acid		0	0	58	6300	4300	..	12
2	6	106.0†	113.4†	6.5					2500					0	0	..	7000	7
3	0	79.4	85.2	6.7	439.0	606.3	27.5	2.42	4525	400	1.026	Alk.	+	+	Gross	7100	5000	..	7	
4	0	44.9	49.2	8.8	459.0	770.3	40.3	13.09	4000	1700	1.014	Acid	+	+	+	53	6800	..	7	
5	0	19.7	21.3	7.4	337.5	516.3	30.7	4.12	4000	800		Acid	+	+	+	57	6000	..	6	
6	0	10.0	11.0	9.9	131.0	207.5	36.9	4.14	3710	1969		..	0	0	0	58	3500	..	6	
7	0	4.4	4.4		26.3	49.4	26.5	1.97	2240	4430		..				55	7300	..		
8	0	2.0	2.0		13.1	23.5	44.2	0.55	3120	2350		..				62	8800	..		
9	6								3010	700										
10	8								2220	850+	1.022	Alk.	+	+	0	56	4000			
11	5	26.1	27.6	5.4					2360											
12									3130		1.023	Acid	0	0	0	49	4000			
13									3130	1450	1.019	Alk.	0	0	0	45	1700	816		10
14									2200	700			0	0	0	52	1500	840	..	
15											1.015	Acid	0	0	0	54	1150	230	..	
16									3200	750+						57	1400	250	..	
17									2800	1650										
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* Intravenous administration (5% sulfamerazine sodium).

† One hour after infusion.

‡ Normal platelet count 1 week later.

§ Days 24 and 28 are omitted as they offered no significant data.

voided specimen of urine following the massive dose of sulfamerazine showed many crystals of the drug and innumerable red blood cells. For the next 48 hours the urine sediment continued to show microscopic crystalluria and hematuria. This patient probably suffered a partial suppression of urinary output, in that, although his urinary output was never less than 800 cc., the diuresis to be expected from his large intake did not occur until the 5th day following his acute episode, when he excreted 4430 cc. of urine. As indicated, the patient was again given sulfamerazine by mouth with no further urinary disturbances.

In a further attempt to detect any harmful effect of sulfamerazine on the kidney, sections of the kidneys from 5 patients who had died of their disease (including the above patient, R. S.), were examined; no renal damage was found which could be attributed to the drug.

Nausea and Vomiting. Eight patients (4%) experienced some degree of nausea and vomiting during the administration of sulfamerazine. Of these, 6 were cases of meningitis and, although the drug was continued, the vomiting gradually subsided. These cases are included in spite of the fact that the vomiting was probably due to the meningitis. The 7th represented a patient suffering with subacute bacterial endocarditis who had previously received sulfadiazine with severe nausea and vomiting and, following 12 gm. of sulfamerazine, it was also necessary to stop the drug because of this toxic effect. The other instance of vomiting occurred in a man with subacute bacterial endocarditis who was given massive sulfamerazine therapy (Table 3).

Dermatitis. Skin rashes, attributable to sulfamerazine, were encountered in 6 (3%) patients. The rash was scarlatiniform in 1 case and morbilliform or maculopapular in the others. In 1 of the patients the rash appeared on the 20th day, after 113 gm. of the drug had been given. Sulfamerazine was stopped and the rash rapidly disappeared, only to reappear when the drug was again started, and at this time it was accompanied by an elevation in temperature of 105° F. The patient subsequently was given sulfadiazine and developed a rash after 2 weeks' medication. In the other cases the rash appeared on the 4th, 5th, 9th and 10th days of treatment.

Fever. Although it is often difficult to determine whether an elevation in temperature above normal is due to the drug or the infection, we have made the diagnosis of drug fever in 5 (2.5%) patients. The fever in these cases was encountered on the 7th, 8th, 10th, 14th, and 40th day of sulfamerazine therapy, respectively. In 2 of the patients the expected fall in temperature was somewhat slower following the withdrawal of the drug than one usually sees in cases with drug fever.

Blood Disturbances. Four patients developed leukopenia (less than 4000 leukocytes per c.mm.) on the 6th, 8th, 9th, and 12th day of sulfamerazine therapy. In 3 the total white blood count soon returned to within normal limits after the withdrawal of the drug. The fourth patient (Table 3) had, in addition to this finding, thrombocytopenia and a fall of neutrophils to 250 per c.mm. A biopsy revealed a generalized hypoplasia of the bone marrow. Within 2 weeks, following repeated

blood transfusions, the peripheral blood picture returned to normal. There were no cases of acute hemolytic anemia or agranulocytosis.

Nervous and Mental Manifestations. In view of past clinical experience with the sulfonamides containing a methyl group² (sulfamethylthiazole, sulfanilyl dimethyl-sulfanilamide), one could presume that sulfamerazine might possibly give rise to certain neuropathologic changes. Welch and his associates,⁴ working with several species of experimental animals, have given particular attention to this matter. It was found that dogs or monkeys, given large doses of sulfamerazine over 30 day periods, showed no evidence of nerve injury; but chickens with high blood concentrations of the drug developed definite nerve lesions, although the changes were no greater than those resulting from lower blood levels of sulfadiazine in the same species.

No case of peripheral neuritis was observed in this study. Two patients presented mental symptoms while receiving sulfamerazine, which were possibly due to the drug. The first, a moderately ill pneumonia patient, became disoriented and quite violent on the 3d day of treatment. The mental symptoms subsided promptly after the drug was stopped. The second patient, a chronic alcoholic, confused on admission, became progressively worse mentally during the time sulfamerazine was given, but, because of the seriousness of his illness, chemotherapy was continued for 5 days and the mental changes cleared while the drug was being administered. Not included in Table 1 is a young girl who was given 15 gm. of sulfamerazine sodium intravenously and following this injection experienced generalized twitchings of the body, simulating an attack of tetany. This phenomenon was interpreted as probably due to a "tubing" reaction, but may have been the result of sulfamerazine intoxication.

Summary and Conclusions. 1. Sulfamerazine was given to 200 unselected patients suffering with acute bacterial infections.

2. Toxic reactions possibly due to the drug appeared in 30 instances (15%), though in many of these instances it was not possible to determine whether they were due to the disease or to the drug itself.

3. Gross hematuria was observed in a single case receiving routine sulfamerazine treatment and 1 additional case receiving massive intravenous therapy.

4. No case of peripheral neuritis was seen, although 2 patients developed transient mental symptoms following sulfamerazine therapy.

5. On the basis of this short series, it appears that sulfamerazine is probably no more toxic than the sulfonamides now in common use¹ and that further clinical trial is justified.

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THE RELATIONSHIP BETWEEN RIBOFLAVIN INTAKE AND
THIAMIN EXCRETION IN MAN*BY CALVIN T. KLOPP, M.D.
NATIONAL CANCER INSTITUTE FELLOWJULES C. ABELS, M.D.
FINNEY-HOWELL FELLOW

AND

C. P. RHOADS, M.D.
NEW YORK, N. Y.

(From the Memorial Hospital for the Treatment of Cancer and Allied Diseases)

IN the course of a recent study of the metabolism and storage of members of the vitamin B complex in patients subjected to surgical procedures, it became necessary to determine their urinary excretion of riboflavin and thiamin. These determinations early suggested that the administration of thiamin alone was followed in some instances by an increased urinary excretion of riboflavin. Therefore, it appeared of interest to investigate this phenomenon further and to determine whether or not the administration of large amounts of thiamin to human beings over a long period of time eventually would induce clinical evidence of riboflavin deficiency. The results of that study form the subject of the present report.

Methods. *Thiamin.* The yeast fermentation method of Schultz, Atkin and Frey⁶ was used. Determinations were made on aliquots of 1, 3, 24, or 72-hour specimens which had been acidified with glacial acetic acid and kept at 10° C. or less in a dark ice chest.

Riboflavin. The determinations were done by the technique of Ferrebee.¹ The urines were collected in the same manner as were those for the determination of thiamin. In certain instances, the microbiologic method of Snell and Strong⁷ was used to check the values obtained by the fluorescence technique of Ferrebee.¹

Tests of Body Saturation of Thiamin and of Riboflavin. The methods used to ascertain thiamin and riboflavin saturation in the body were those of Holt and Najjar.^{4,5} Both these tests measure the portion of administered vitamin retained by the body under controlled conditions.

Diets. All short time experiments (in which measurements were carried out over a period of a few hours) were done in fasting subjects. The subjects who were studied over a period of several days took 2 types of diets: (a) Those individuals who were not hospitalized continued to eat a normal diet with the following exceptions—no synthetic vitamins, medications, alcohol, beer, or glandular meats. Their meat and milk intake from day to day was relatively constant. (b) The remaining subjects who were hospitalized were given a diet in which the protein, carbohydrate, and fat intakes were constant. Intake of medications, alcohol, vitamins and glandular meats likewise was restricted.

Clinical Material. The clinical material consisted of the following groups: A. Three hospitalized patients were used in the thiamin tolerance experiments.⁴ One had melanoma with extensive metastases; the second had uterine fibroids; and the third, carcinoma of the rectum.

B. The effect of large amounts of thiamin given daily for from 2 to 67 days was ascertained on 13 individuals. Of these, 8 were normal, and the remainder

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were hospitalized patients who presented the following disorders: 1, dysmenorrhea of unknown cause; 1, atrophic gastritis; 2, hepatic cirrhosis; and 1, Paget's disease of bone.

Of this group, 6 of the 8 normal individuals were later given larger amounts of thiamin, and for a longer period of time, in an attempt to induce in them a riboflavin deficiency.

C. The last group consisted of 4 individuals who received several injections of thiamin over a period of 4 hours only. One individual was normal, the second had carcinoma of the breast with extensive metastases, the third lymphatic leukemia, and the fourth had melanoma with distal metastases.

Results. *A. Experiments to Test the Effects of the Administration of Thiamin on the Excretion of Riboflavin over a Period of 4 Hours.* The thiamin tolerance test of Holt and Najjar⁴ was carried out in 3 individuals. This test was repeated in 2. The content both of thiamin and of riboflavin was determined in each urine specimen. These measurements indicated that, in all instances, the injection of thiamin alone was followed by an increased excretion of both thiamin and riboflavin. Moreover, the increased excretion of riboflavin was independent of the urine volume (Table 1).

TABLE 1.—THE URINARY EXCRETION OF RIBOFLAVIN AFTER THE INJECTION OF 1 MG. OF THIAMIN

Subject	Fasting output*		After thiamin administration							
			0-½ hr.		½-1 hr.		1-2 hrs.		2-3 hrs.	
	Mg./ml.	Mg./hr.	Mg./ml.	Mg./½ hr.	Mg./ml.	Mg./½ hr.	Mg./ml.	Mg./hr.	Mg./ml.	Mg./hr.
E. T.	0.13	13	0.48	36	0.09	5	0.03	6	0.11	12.0
	0.16	15	0.37	34	0.30	8	0.07	11	0.10	14.0
R. B.	0.12	9	0.34	21	0.18	7	0.06	12	0.05	19.0
	0.20	8	0.28	12	0.37	9	0.16	10	0.05	14.0
F. S.	0.33	15	0.63	15	0.46	7	0.50	9	0.50	7.5

* 15 hours after the last meal.

Since the "riboflavin" excreted was measured by a fluorescence method,¹ it was possible that the parenteral administration of thiamin was followed by an increased excretion of material which had the fluorescent property of riboflavin, but nevertheless was not that vitamin. It was necessary, therefore, to demonstrate that this fluorescent material actually was riboflavin, and not some degradation product of thiamin. The fluorescent properties of thiamin itself are very much different from those of riboflavin.³ To date, the only metabolic product of thiamin known to appear in the urine is a pyrimidine compound which has the ability to accelerate yeast fermentation.^{2,11}

Accordingly, large amounts of this pyrimidine accelerator of yeast fermentation (2-methyl-5-methoxyethyl-6-aminopyrimidine) were added to urine samples whose "riboflavin" fluorescence was known; this addition did not effect the amount of fluorescence observed.

There still remained the possibility, however, that the parenteral administration of thiamin resulted in the excretion of another but unknown fluorescent metabolite of thiamin or of a material not related to that vitamin and also not related to riboflavin. For this reason, measurements of riboflavin in urine specimens of individuals who received thiamin were made both by the fluorescence technique of Ferrebee¹ and by the microbiologic method of Snell and Stroug.⁷ The

results of all determinations were in good agreement. It was evident, therefore, that the administration of thiamin to these subjects was followed by an increased excretion of a substance which had at least two properties of riboflavin: its fluorescent characteristics and its ability to accelerate the growth of *Lactobacilli casei* (Table 2).

TABLE 2.—EFFECT ON THE EXCRETION OF RIBOFLAVIN AFTER THE ADMINISTRATION OF 1 MG. OF THIAMIN TO SUBJECT F. S. COMPARISON OF RESULTS OBTAINED BY DIFFERENT METHODS

	Determination by	
	Fluorescence technique, mg./ml.	Microbiologic technique, mg./ml.
Fasting level	0.33	0.25
0-½ hr.	0.63	0.63
½-1 hr.	0.46	0.45
1-2 hrs.	0.50	0.45

B. Experiments to Test the Effect of the Daily Administration of Thiamin on the Excretion of Riboflavin. Since an increased excretion of riboflavin followed the injection of as little as 1 mg. of thiamin, it seemed possible that the urinary excretion of riboflavin after the daily administration of large amounts of thiamin might induce a serious loss of riboflavin. To test this possibility, 13 subjects were studied. The excretion of riboflavin in the urine of these individuals was measured each day during a control period of from 3 to 7 days. At the end of these periods, each individual was given thiamin chloride in amounts from 10 to 80 mg. per day and measurements of the excretion of riboflavin were continued. An increased riboflavin output was considered significant when: 1, an increased concentration as well as an increased total amount was excreted; 2, the increase was at least 40% above the average control value; and 3, the increase persisted for more than one 24-hour period.

The results obtained in these individuals were less consistent than were those of the short experiments previously described. Four of the 13 subjects took a constant diet, while the others were allowed to continue their routine work and diet under the conditions previously described. Of the 13 subjects given thiamin, 8 excreted temporarily increased amounts of riboflavin. The remaining 5 did not excrete significantly increased amounts; 4 of these were normal individuals and the fifth was a patient with cirrhosis of the liver.

The results obtained indicate that the maximum increase in total excretion of riboflavin in those 8 instances in which an increase was observed, varied from 40% to 560% and the average increase of this group was 225%. The increase in the concentration of riboflavin varied from 43% to 520%, and the average was 180%. No individual maintained the increased excretion for more than 8 days despite continued administration of thiamin.

An increased amount of thiamin was given to 3 normal subjects after the first period of increased riboflavin excretion was over. In all, a second but smaller increased excretion of riboflavin followed the augmented thiamin administration. In 2, a further increase in the

amount of thiamin was followed by a third period of increased excretion of riboflavin. On the other hand, in 2 other subjects in whom no initial increased excretion of riboflavin had been noted after the first administration of thiamin, no increased excretion could be induced by giving even larger amounts of thiamin. Many of the determinations of riboflavin in the urines of this group of subjects were made both by the fluorescent method of Ferrebee¹ and by the microbiologic method of Snell and Strong.⁷ The values obtained by both methods checked well (Table 4).

TABLE 3.—EFFECT OF THE DAILY ADMINISTRATION OF THIAMIN ON THE EXCRETION OF RIBOFLAVIN

Subject	Duration of control period, days	Average daily riboflavin excretion during control period		Amount of thiamin administered parenterally		Maximum excretion of riboflavin after thiamin		Duration of increased excretion, days	% increase in excretion of riboflavin after administration of thiamin	
		Mg./ml.	Mg./24 hrs.	Average daily dose, mg.	Duration of administration, days	Mg./ml.	Mg./24 hrs.		Concentration	Total excretion per day
A. T.	3	0.18	400	10	3	0.35	1100	3	95	170
M. Z.	3	0.35	480	40	2	0.50	900	2	43	88
E. H.	4	0.25	400	30	2	0.50	1600	3	100	300
N. N.	6	1.00	1200	30	53	2.30	2900	7	130	140
M. P.	6	0.34	320	35	67	0.42	450	0	23	40
G. F.	6	1.30	1200	40	7	1.50	1300	0	15	8
J. J.	5	0.75	900	20	10	0.70	1200	0	0	33
R. H.	5	0.40	600	50	41	2.50	4000	7	520	560
R. M.	4	0.32	900	30	2	0.37	900	0	16	0
F. B.	4	0.47	375	50	17	0.72	560	7	52	49
H. F.	8	0.19	340	80	13	0.25	480	1	31	41
M. H.	5	0.18	210	50	67	0.75	800	8	320	270
E. B.	3	0.18	550	20*	7	0.35	900	7	190	160

* By mouth.

TABLE 4.—COMPARISON OF VALUES OBTAINED BY DIFFERENT METHODS DURING THE PERIOD IN INCREASED EXCRETION OF RIBOFLAVIN AFTER THE ADMINISTRATION OF THIAMIN

Subject	Determination by	
	Fluorescence technique, mg./ml.	Microbiologic technique, mg./ml.
1	0.76	0.72
2	0.68	0.65
3	0.68	0.66

C. Experiments to Test the Possibility that the Daily Administration of Large Amounts of Thiamin Might Deplete the Body Stores of Riboflavin. Since the administration of thiamin was followed by an increased excretion of riboflavin in 8 of 13 subjects studied, it seemed possible that continued administration of thiamin eventually might deplete the body stores of riboflavin and produce clinical evidence of a deficiency of that vitamin. This deficiency might be manifest also by a continued decrease in the amount of riboflavin excreted, and by an abnormal retention of riboflavin when that vitamin was administered (the riboflavin tolerance test of Holt and Najjar⁸).

To study this possibility, 6 normal individuals were given parenterally from 30 to 60 mg. of thiamin chloride per day for from 11 to 73 days. At the end of these studies none of the subjects had developed clinical signs of riboflavin deficiency. Only 1 excreted less riboflavin than he did during periods before the administration of thiamin. The other 5 subjects excreted amounts of riboflavin similar to those during

the control period. None of the 6 showed any increased retention of riboflavin as determined by the riboflavin tolerance test (Table 5).

D. Experiments to Test the Effect on the Excretion of Riboflavin of Multiple Small Doses of Thiamin Over a Short Period of Time. It has been shown in a previous section of this communication that an increased output of riboflavin followed within a few hours the injection of 1 mg. of thiamin to fasting subjects. On the other hand, when thiamin was administered daily over a period of several days, no sustained, increased riboflavin excretion followed. Hence, it appeared desirable to ascertain the effect on the excretion of riboflavin of multiple 1 mg. doses of thiamin given at intervals of from 30 to 60 minutes.

TABLE 5.—EFFECT OF THE DAILY ADMINISTRATION OF THIAMIN OVER A PROLONGED PERIOD OF TIME ON THE EXCRETION OF RIBOFLAVIN IN THE URINE

Subject	Duration of control period, days	Average excretion of riboflavin during control period		Amount of thiamin administered parenterally		Average excretion of riboflavin at end of experiment		% retention of test dose of riboflavin at end of experiment
		Mg /ml.	Mg /24 hrs	Average daily dose, mg.	Duration of administration, days	Mg /ml	Mg /24 hrs.	
N. N.	6	1 00	1200	30	68	0 80	1200	58
M. P.	6	0 34	320	35	73	0 34	312	50
R. H.	5	0 40	600	50	42	0 70	970	40
M. H.	5	0 18	210	50	72	0 13	180	64
F. B.	4	0 35	540	60	18	0 28	470	46
H. F.	8	0 23	408	60	11	0.15	220	48

Measurements of riboflavin excretion were made in the urine specimens collected each hour from 4 individuals who received 1 mg. of thiamin every 30 or 60 minutes for from 4 to 5 doses. In 2 of the 4 subjects an increased excretion of riboflavin occurred. In one this increase persisted for only 2 hours, whereas in the other the increased riboflavin output was maintained for the duration of the experiment.

This increased excretion of riboflavin in 2 of the 4 subjects compares well with the incidence in which the phenomena was noted in the 13 individuals given thiamin over long periods of time.

Discussion. From the data presented it would appear that in certain persons a relationship exists between the thiamin intake and riboflavin excretion. The existence of a relationship between these 2 vitamins already has been demonstrated in experimental animals. The transient mobilization of riboflavin from the tissues into the liver of thiamin deficient rats has been found to be considerably impaired, but that metabolic defect can be corrected when adequate thiamin supplements are administered.⁵

It is possible, therefore, that the administration of large amounts of thiamin to the subjects included in the present study might have initiated a similar transfer of riboflavin from the tissues into the liver, and in the course of that shift a portion of the compound was spilled into the urine. Evidently, the magnitude of this loss was not great enough to produce any clinical evidence of riboflavin deficiency nor could a deficiency of that vitamin be detected by the tolerance test used in this investigation.⁵

Recent studies have demonstrated¹⁰ that rats whose diets were free of all members of the vitamin B complex except for small amounts of

riboflavin (2 μ g. per day) gained weight at a slower rate and had a higher incidence of mortality when large supplements of thiamin were fed. However, these effects of thiamin were not noted when the riboflavin supplement was increased to 10 μ g. per day.

Clinical evidence of interrelationship between members of the vitamin B complex have been noted by others. Sydenstricker called attention to the fact that the administration of single B vitamins will stimulate the appearance of lesions commonly associated with a deficiency state of other members of the B complex.⁹ However, it would appear from the present study that a deficiency of riboflavin could not be induced readily in individuals who probably were not deficient in vitamins B by the long continued administration of thiamin.

Summary. 1. The administration of thiamin to human beings in many instances is followed by transitory increased excretion of riboflavin in the urine. No explanation for the relationship is at hand.

2. It has not been possible to induce either clinical or chemical evidence of riboflavin deficiency in these individuals by the daily administration of large amounts of thiamin for as long as 73 days.

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PROGRESS OF MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
IRVING J. WOLMAN, M.D.

PASSED ASSISTANT SURGEON (RESERVE), UNITED STATES PUBLIC HEALTH SERVICE

THE CHILD IN WAR

BY IRVING J. WOLMAN, M.D.

EVERY environmental change has its reflection on the child living within that environment. There is hardly a child on the face of the globe whose life is not being altered in some way by the current war. To a greater or less degree each must contend with shortages of food and other necessities, infectious agents on the move, abnormal emotional experiences, altered home conditions and family relationships, and all kinds of deviations from a peaceful normal pattern of living. The modern pediatrician cannot escape becoming concerned over the expected harmful effects of this war upon the children now enduring its hardships, and so quite naturally he turns back to the records of the last great war to discover what general trends and principles were noted by the child specialists of 2½ decades ago.

The medical papers published during World War I and afterwards fail to reconstruct the full picture of the War's effects upon the European child. Scientific studies on health and growth are surprisingly limited in numbers, and most seem incomplete and inadequate when judged by current standards of scholarship. For example, there are many references to such disorders of malnutrition as rickets, but the diagnostic criteria and the presentation of control statistics are as a rule not published. And few of the studies contain the complete body of data or even a representative fraction, so that the reader may judge for himself the validity of the author's conclusions. Of course, inside of combat zones and occupied territory the military exigencies may block all opportunities for the collection of good scientific records, and statistics on mortality and morbidity in populations churned up by war are subject to suspicion as to completeness and reliability. Even in less violently disturbed areas most doctors are too occupied with more pressing and urgent tasks to note down in quantitative terms the full mass of their observations. Furthermore at the time of the last war much of the present understanding of vitamins and nutritional requirements was perhaps dreamed of but otherwise absent, and the fundamental standards by which we try to evaluate growth and nutrition were still in the nursery stage of development. Together with these limitations of the pediatric history of World War I, no medical scholar has attempted an exhaustive detailed

compilation and interpretation of original source material. The closest approach to this ideal treatise are some of the chapters in the monographs on public health during the war sponsored by the Carnegie Endowment for International Peace. The volumes from Germany¹¹ and from Austria Hungary¹² are richer in pertinent information than those from France⁴ and Italy;³⁹ but unfortunately the contributing authorities have as a rule neglected to annotate their generalizations and impressions with references or footnotes.

For the present review, the aim has been, not to compile any sort of comprehensive compendium, critical or uncritical, but rather to summarize briefly a few of the more objective and scientific reported contributions. The effort was made to restrict the selected papers to those dealing with child health and growth. The topics of nutrition, feeding and epidemiology, about which much can be found, are merely touched upon. The latter part of this review describes a few important reports from the present war. One cannot but hope that those medical workers in the child health field on the other side of the water will continue to collect and record significant observations with equal assiduity and under circumstances as similar as possible to those of the pre-war period, so that later on it will be possible to draw comparisons between the contemporary child's wartime status and that of peacetime years.

The Effect of Malnutrition Upon Intelligence and Behavior. One of the best studies made in this field was that of Blanton,⁵ who studied the entire school population of a German city near the war zone. While stationed at Trier (population 55,000) with the American Army of Occupation, he made a psychiatric survey of some 6500 school children, ranging from 5½ to 14 years of age. The food blockade had not yet been lifted and hunger and malnutrition were still widespread. In March 1915 the German Government had taken control of the nation's grain supply, and by 1916 every variety of food except green vegetables was being rationed. The bread, which was everybody's food, became progressively more coarse, and by 1918 the rye and other flours were present in essentially unmilled form. Rubner⁴⁰ showed that this inferior bread not only causes intestinal disturbances but yields to the digestive tract of the adult but 60 % of its protein and 85 % of its calories. With young children the loss by failure of absorption was even greater. Bruns and Hartman^{9,10} reviewed the meals of 2413 school children in Trier and found that only 68 were receiving milk. A child's official diet for 1 day was as follows:

Breakfast: 95 % unmilled rye bread, marmalade of turnips and beet molasses.

10 A.M.: Bread, marmalade.

Noon: Potatoes, war soup containing little or no fat, perhaps bread.

4 P.M.: Bread, marmalade.

6 P.M.: Potatoes, soup, bread.

On Sundays sausage or herring and butter or margarine were added. Nearly every family supplemented this starvation ration with food purchased from illegal sources; but the poor could not afford enough extra items to procure anything near an adequate diet. It was found that approximately half of the children had been on starvation rations for 2 to 3 years. During the winter of 1918-19, the American observers encountered an appreciable amount of sickness among the children, the most common infections in the order of frequency being influenza, pneumonia, tuberculosis and middle ear disease. Comprehension of lessons was found poor and slow, their attitude disinterested and their wits dull. It was

believed that the fatigue and restlessness were caused not alone by malnutrition but by actual hunger as well, since many of the children came to school from homes lacking food for breakfast. In striking contrast the youngsters from more prosperous households were bright, strong and active, and seemed to do well in their classes. To be sure there had been environmental factors other than the chronic food shortage to disturb children. Thousands of troops and many wounded had been kept in the city, often being quartered temporarily in the school houses. Most of the male teachers had been called to military service. Many fathers were away at the front, and home discipline was consequently relaxed. Numerous air raids and the even more frequent air alarms were continually interrupting the children's activities both in school and at home. But the most important single factor in retarding their educational progress seemed to be the poor nutrition and physical starvation of the children themselves.

Effects of War Upon Children's Mental Condition. Can malnutrition cause feeble-mindedness? To answer this question Blanton examined every retarded and dull child to be found in the school system, using as criteria low school grades and the results of a modified intelligence quotient test. Marked mental retardation regarded as due to malnutrition alone was found in 135 (2.08%), and malnutrition plus infection found in an additional 2.57%. Another group (2.74%) was judged as being scholars of borderline ability who under favorable circumstances could manage to keep abreast of the class by dint of hard work, but when handicapped by lack of sufficient food could not keep up, even though the pace of teaching was appreciably slower. Thus about 8% of all the children showed signs of serious injury to the nervous system due to starvation. Blanton made a thorough search of the school population for evidences of psychologic and psychiatric disorders. Among the 6500 children there were but 15 truants, 25 extremely nervous and emotionally unstable, 6 epileptics, 1 dementia precox, 5 with organic lesions and only 2 with true neuroses, both being highstrung timid girls reacting in this fashion to the deaths of their fathers on the battlefield. The percentage of major nervous and mental disturbances which could be attributed to the war was therefore small indeed. Many children however did display nervous symptoms of mild degree. They were afraid to go to sleep; dreamed with terror about bombings; tossed restlessly all night. Some worried constantly over relatives killed or captured; many would cry whenever war or their fathers were mentioned. No instances of incoherent stuttering or stammering were present, but the majority of children in the first and second grades suffered from mild speech defects such as slurring and lispings, indicating that the fine coordinations essential for good speech were being interfered with. This behavior was more conspicuous among the underweight and ill-fed youngsters.

Thus more than 90% of the children endured the 3 year starvation period without suffering any major emotional disorder or permanent deterioration of mental capacity. The minor disturbances, though common, were expected to clear up as the restrictions on food became eliminated and life returned to a more peaceful level. Many parents told Blanton that their children's slight terrors and nervousness began to fade away soon after the Armistice was signed.

Effects of War Upon Infant Health. During the first 2 years of the war, no change in weight or length of newborn German babies was observed in spite of the fact that many mothers were showing evidences of faulty nutrition as a consequence of the beginning food shortage.²⁹ But from the

third war year on, the birth weights of newborns regularly fell a little, being some 50 to 100 gm. below the peacetime level. The figures from Oppelm showed the mean weight of newborns in 1917 and 1918 to be below 3000 gm.²⁹ Recovery from the physiologic loss of weight in the neonatal period was slowed somewhat, and the frequency of stillbirths, prematurity and congenital debility of the newborn increased a little. But it was the general impression among obstetricians as stated by Sellheim²⁹ that even when a mother undergoes great physical strain and privation during the entire pregnancy the fetus would show few evident signs of injury and that the baby as a rule would appear in good condition when born.

In blockaded countries the infants and children suffered great malnutrition as a consequence of the lack of cow's milk and other important nutrient foods. Infantile diarrhea and other digestive disorders, scurvy, rickets, skin diseases, intestinal parasites, influenza, the acute exanthems, tuberculosis, and every sort of contagion and nutritional disturbance crowded the out-patient clinics and hospitals in tragic reflection of the mass starvation and dearth of essential supplies. For summaries of these and related epidemiologic problems in the European countries the reader is referred to the above-mentioned publications of the Carnegie Endowment for International Peace. A good introduction to the problems of feeding the hungry people both during and after the Great War will be found in the same series of monographs, in publications from relief organizations such as the American Red Cross^{2,31,33,52} and the American Food Relief Administration,⁵⁵ and in the paper of Mason.³⁶ Infant mortality statistics from countries actively engaged in the war at close range showed an increase during the war period and until shipments of food were sent in after the blockade was lifted. Data from some of the warring countries are shown in Table 1:

TABLE 1.—DEATH RATES FOR INFANTS 1 YEAR AND UNDER (PER 1000 LIVE BIRTHS)

	France ¹	Austria ²¹	Budapest ⁷	Italy ²⁹
1911				
1912	153.8	201.4	161.5	
1913	105.0	166.6	138.3	
1914	110.2	179.9	146.2	135.1
1915	109.1	169.3	154.9	
1916	113.0	210.7	174.3	127.3
1917	112.1	198.3	152.8	142.4
1918	131.4	188.2	185.4	146.2
1919	151.1	191.5	178.0	142.6
1920	124.9	157.1	156.4	181.5
1921-23	123.7	159.2	181.0	
	98.5	123.6

The data in Table 1 were reported from nations at war, some for a time being invaded or occupied. No correction has been made for the abnormally low birth rates which were observed from 1914 through 1919.¹⁸ For this as well as other considerations inherent in the sources of the data, the columns should not be compared one with another, but only viewed vertically. Bókey and Juba,⁷ who presented the Budapest figures, comment that the supply of cow's milk and other baby foods was so scanty there that had it not been for mother's milk many more babies would not have survived; they observed that the percentage of infants being raised on breast milk had gone up significantly in comparison with the previous years of peace.

For many years the children born under the trying conditions of the

hunger blockade were looked upon by the local physicians as a handicapped group, unusually susceptible to illness and slow to convalesce.²⁹

Glands of Internal Secretion. Curiously, after the war had been over for several years there came reports from scattered areas in Germany of goiters developing in school girls and adolescents. Lill³² reported from Wurzburg, a community with normally a low goiter rate, that the incidence of thyroid enlargement had risen in the years 1922 through 1925 from a usual rate of 1.1 % to 2.8 % up to between 3 % to 11 % in the various age groups of the school girls. In Mannheim, where goiter once had been uncommon, Stephani⁵¹ found that, in 1924-25, 35 % of the boys and 37 % of the girls had visibly enlarged thyroids, often tumor-like. No explanation was apparent to the observers for this disturbance of thyroid function.

Rickets, especially the late variety in children over 5 years of age, became common in the clinics of Germany and Austria in the late war and post-war years.^{16,26,29} For example, Engel¹⁶ in Berlin encountered some 63 cases of late rickets in 1916, 26 in 1917, 62 in 1918 and 141 during 1919. Undoubtedly faulty food and hygiene played major rôles in the causation of this osteomalacic disturbance, but perhaps additive factors of hormone character were active also.

Starvation may retard the onset of menstruation, according to Calmette¹² and Heuyer.²⁵ The conclusion was based on studies of the French children of Lille who had experienced $4\frac{1}{2}$ years of semi-starvation during the German occupation. When surveyed after the Armistice all were said to show retardation of weight, height and chest circumference, though measurements were not published. Tuberculosis was found to be much more prevalent than before the war, judged by chest findings and enlarged cervical nodes. During the occupation, scurvy, peripheral neuritis and pellagra had been common,³⁰ and several outbreaks of dysentery had occurred. Calmette's examination showed that but 20 of 100 girls at the age of 18 had as yet established a regular menstrual rhythm, and Heuyer found 8 out of 12 of that age who were not yet regular. Heuyer stated also that signs of hypothyroidism were frequent.

Tuberculosis. An increased incidence of childhood tuberculosis was reported from all parts of Germany³⁸ and Austria Hungary.⁴² Thus in Stettin²⁹ the tuberculosis death rate for children which from 1910 to 1915 had ranged between 0.35 to 0.40 per 1000, had tripled to 1.2 in 1916-17, 0.94 in 1917-18. Equally striking are the data on the increased frequency of positive reactors to the Pirquet skin tuberculin test from Berlin,¹⁵ Charlottenburg,⁵⁶ Vienna,⁴⁸ Rostock²⁸ and Munich.³ Among children in institutions and of the low income group in various cities during the war, the positive reactors ranged from 20 % to 30 % at the early age of 2 years—taking the figures for this age as an illustration—whereas prior to 1914 the incidence in the same communities was between 9 % to 12 %. Bartschmid's³ values for Munich were as follows:

TABLE 2.—TUBERCULOSIS INCIDENCE IN MUNICH

Age of children (in years)	Percentage of positive reactors	
	1912-1914	1915-1919
1	12 8	13 9
2	19 6	24 8
3-4	25 8	44 1
5-6	32 7	51 7
7-8	47 6	54 2
9-10	43 6	63.3
11-12	50 0	56 6
13-14	64.9	57.4

Schick and Wagner⁴⁸ record the appearance of great numbers of children with severe scrofula and malignant forms of pulmonary consolidation in the University pediatric clinic of Vienna in the years after the war. Langstein and Rott²⁹ found that where poverty was greatest, food, clothing and fuel most inadequate and sanitary facilities very rudimentary or absent, that there the spread of tuberculosis among the children was found most rampant. They noted that the years of financial depression and currency inflation which followed the war were even worse than those of the war itself. All observers agreed that the fundamental factors responsible for the enhanced spread of childhood tuberculosis were diminished bodily resistance consequent to malnutrition and poor hygiene of living plus augmented opportunities for contact with the growing number of unhospitalized active cases in the adult population.

Results of Starvation Upon Size and Growth. That children thrive poorly during underfeeding or famine is a truism requiring no substantiation from authority. Of the many reports from the World War experience only a few will be cited. Davidsohn¹⁵ presented data on physical measurements of orphanage children in Berlin, contrasting 300 youngsters of 1908-09 with a comparable group from the same institution in 1919. The study showed that the 1919 boys weighed 15% less and were 7.2% shorter, while the girls weighed 24% less and were 6.4% shorter. Expressed in chronologic terms the boys of 1919 corresponded in size to boys $1\frac{1}{2}$ years younger of peacetimes, and the girls corresponded in size to girls $1\frac{1}{4}$ years younger. Interestingly in Davidsohn's group of children the weight was affected adversely to a greater degree than was the length, whereas in Pfaundler's⁴¹ series the opposite relationship was encountered. In Munich⁴¹ 2500 children entering school in 1917-18 were measured and the data compared with those for 1912. The average weight of the children was found to be 4% less than before the war, the height 7% less. The differences were especially noteworthy among children from the better social classes. Kaup²⁷ studied an elder age group in the same city (Munich). He compared the measurements on over 100 boys 14 years of age in 1920 with the data on a similar group obtained in 1913. At the later period the length difference averaged -2.2 cm. (1.4%), the weight averaged -1.5 kg. (3.8%). The deficit in length for these older children was thus relatively less than had occurred with Pfaundler's more youthful population sample.

Will children after being starved for several years always be smaller than their normal contemporaries, or will the temporarily slowed growth impulse accelerate to correct for the deficit once a liberal intake of food is provided? A partial answer to this question lies in the observations on the excellent nutritional response of war-stricken European children to good food and hygiene after the war. From 1919 through 1921, with the aid of financial contributions from all over the world hundreds of thousands of semi-starved youngsters were sent to more favorable environments for recuperation and upbuilding. Scores of reports testified to the rapid recovery, sudden growth and restoration of visible signs of good health. For example, Abderhalden¹ described a group of 27 Austrian children aged 8 to 14 years received in Magdeburg. In 8 weeks the average weight gain was 3.2 kg. and the average height increase was 2.8 cm. Bloch⁶ reported on 30 severely undernourished children sent from Halle, Germany, to Rickenbach, Switzerland. In a little more than a month these put on weight averaging 5.3 kg. (11.7 pounds) and the hemoglobin had climbed more than 10 points in mean value, ranging from 38 to 61 on admission

and between 54 and 72 on discharge. Analysis of Reischl's⁴⁴ figures on 1543 Austrian children sent to neighboring rural camps for 1 to 2 months reveals an average gain of 0.3 kg. per week. When one recalls that the rate of weight gain for normal healthy American children amounts only to about 0.05 kg. weekly,²² the spectacular growth curves of Europe's children are eloquent evidences of the state of nutritional depletion of their tissues and the beneficial effect of more favorable diet. Further corroboration is found in the reports of Schlesinger⁴⁹ and Rössle and Böning⁴⁵ that by 1923 most of the weight and length deficits in children of school age had become corrected and compensated.

Wolff,^{5a,b} school medical officer in Berlin until the Nazis took over, reviewed with careful statistical technique his measurements of the children entering and leaving the school system over a 20 year period, in order to ascertain whether those born during the lean years of the war showed any signs of permanent physical retardation. The mothers of these children had been in poor nutrition during their pregnancy and breast nursing periods, and the children themselves had failed to receive adequate diets during the first few years of life. When they first came to school at the age of 6 years (in 1924-26), both the boys and the girls were 2.5 to 4.0 cm. shorter in average height than were those of the same age who entered in 1927-1928. The weights showed a similar difference of 0.5 to 1.0 kg. in favor of the later born. The gross difference between the means of the entrance in 1924 and in 1932 ranged from 5.9 to 6.5 cm. in height and from 1.07 to 1.57 kg. in weight. These values were shown by calculation to be statistically significant.

Wolff studied these same children 8 years later when they were 14 years old and graduating from the school. At this age the mean weight and height proved to be in the same range as the values for graduates in the years immediately preceding, which were taken as normal controls. Thus by puberty the group of children born during the period of extreme food shortage had caught up with and corrected their growth deficit which had been still detectable at 6 years of age.

The Pirquet System. No review of child feeding in relation to malnutrition would be complete without a reference to the Pirquet system^{13,21,43,47,49,50} even though it is now essentially of historic interest. For when World War I was over this system under von Pirquet's direct supervision became an integral element in the administration of food relief to the children of the Central Empires, some 420,000 in all, and stimulated critical discussion all over the world. There were four principal features. The first took 1 cc. of breast milk of composition 3.7 % fat, 6.7 % sugar and 1.7 % protein (energy value 0.67 cal.) as the elemental unit of food value against which all other foods could be measured. The name given this unit was the "nem" (Nahrungs-Einheit-Menge). Tables were prepared expressing common foods in terms of nems or multiples thereof, named by neologisms such as decinem and hektodem. In the relief kitchens which supplied supplementary meals to the undernourished children the food needs of the expected individuals were estimated and added, and then menus prepared to meet the total number of nems required. Each child's portion contained the exact calculated amount of food. Each child ate his complete portion, and there was no waste.

Theorizing that food absorption was proportional to intestinal surface area, and that this in turn was proportional to sitting height, Pirquet proposed that the square of the sitting height be taken as the physical measurement most indicative of the child's nutritional needs. Food re-

quirements could be reckoned in terms of nems per Si² (sitting height), with specific allotments made for minimum metabolic needs and for growth, fat deposit and muscular activity.

The third feature was a new index of the state of nutrition termed "pelidisi." This was derived by taking the cube root of 10 times the body weight in grams, dividing by the sitting height in centimeters and multiplying by 100. The range from 90 to 94 pelidisi was interpreted by Pirquet as average, below 90 undernourished and above 94 well nourished. The children of the various Austrian provinces were all measured in these terms and comparisons drawn between their nutritional status before and after receiving food relief.

The fourth feature standardized the subjective or clinical evaluation of the child's nutrition in terms of the coined word "sacratama." The results of the physical examination were described under the consonantal headings of *sanguis* (blood), *crassitudo* (fat), *turgor* and *museularis*, with the vowels used as symbols to denote deviations from normal, and a code of numbers to summarize these already condensed derivations. The lack of uniformity of assessment among groups of experienced physicians led even Pirquet to admit that this subjective approach was not very accurate or useful.

As Faber^{17a,b,c} and others pointed out, grave doubts as to scientific validity attend most of the basic propositions. Sitting height will fluctuate with the state of contraction of the gluteal muscles.^{19,20} Pelidisi reflected slight variations in length with much more emphasis than it did appreciable changes in weight. The many neologisms caused confusion. The nem seemed to be no advance over the more familiar calorie, and the resemblance of the pelidisi series to the percentage scale was confusing and misleading. The Pirquet system was judged brilliant but imperfect by the many clinics which gave it a trial, and the familiar height-weight tables retained as being more practical and trustworthy.

Effects of the Current War. At this writing children all over the world are experiencing every kind of deviation from normal ways of living due to war. In some countries such as Russia, China and other dominated territory these changes and hardships are much more extreme than in others more removed from the actual battle areas. That their physical, nutritional and psychologic conditions will be influenced goes without saying, but years must pass and data and critical evaluations accumulate before a comprehensive and historically sound analysis of this war's effect upon child health can be prepared. The lay press has featured innumerable articles on the conditions of Europe's children^{14a} but medical reports to date have been relatively few.

Wattie⁵⁷ summarized the public health situation in Glasgow during 1941, and the report merits attention as being no doubt somewhat representative of conditions obtaining in other British cities. Infant mortality has been rising, the rate being 93.1 in 1938, 82.7 in 1939, 109.2 in 1940 and 131.5 in 1941 (data calculated for the first 6 months of each year). Analysis of the data showed this rise to be due in large measure to a growing number of deaths from maturity and from congenital malformation. Pneumonia, bronchitis and pertussis were on the increase. It is interesting that, following the enemy air raids on Glasgow during March and April 1941, a great number of cases of whooping cough were reported, the children having contracted the disease while congregated in air raid shelters night after night. Scabies, diphtheria and cerebrospinal fever were unusually widespread. On the psychologic side comes the report that the great

majority of small children have gone through the period of intensive bombing without any neurotic symptoms or similar ill-effects. With the older children more juvenile delinquency was being observed, the increase in convictions being about 40 %. This figure represents about 2 % of the whole age group. Home discipline is lax because many fathers are in military service and mothers occupied with war work, and the schools have been functioning on a part-time basis.

The British government is taking special steps to maintain good nutrition among children. Provision has been made for outdoor camps and extra milk, fruit juices, hot breakfasts and good lunches at school. English children, especially those from the slums, show marked benefit from the government's program.⁸ Mackay³⁴ found an increase in borderline anemia in slum children. Milligan and Lewis-Fanning³⁷ studied the growth and physical strength of 133 boys 11 years old in Glossop from January-February to September 1941, and found that the growth in weight was 48 % and in height 79 % of pre-war standards. Payne and Topley⁴⁰ studied 27 children in a base hospital by the vitamin C saturation technique and noted that 14 were markedly lacking this vitamin. Harris,²³ using a similar technique, compared data from school children in the spring of 1941 with the vitamin C status of children of the same age and social background in the spring of 1939. An appreciable drop in the saturation level was detected and attributed to the diminished supply of available fresh fruits.

Stuart⁵³ and Stuart and Kuhlmann⁵⁴ have published a model report on child health conditions existing in southern France in the first 6 months of 1941. They studied the children of Marseilles by the most modern scientific methods, collecting anthropometric, roentgenologic, laboratory and dietary data to serve as a base line from which to measure the progress of these children's growth under the restrictions and handicaps of war conditions. There were approximately 200 children under 2 years of age in the random sample studied, on diets most of which had been deficient in vitamins, animal proteins and calcium for a year preceding. It had been planned to reexamine the children at 6 months' intervals to note the irregularities and disturbances which might develop, but the turn of circumstances occasioned by the recent German occupation of all of France presumably has halted the work on this project. Stuart and Kuhlmann published the data of the initial survey, recording body weight, size in terms of recumbent body length, standing height, chest circumference and pelvic breadth measurements, and muscular and osseous development as measurable by the roentgenogram. In comparison with the accepted standards for normal American children of equal age, the French children were found a little smaller and of short and stocky build. The data for body weight did not support the view that any large proportion were underweight to a marked degree, though the absence of any previous examination made it impossible to determine whether their rate of growth had been slowed during the months preceding the survey. A far greater irregularity obtained in the patterns of bone calcification than would be expected normally, and this was attributed to environmental factors. Mild to moderate rickets was found in 13 of 27 infants under 22 months. Failure of these babies to receive a vitamin D supplement was not primarily a result of war but rather was due to the absence of any antecedent national public health program of education of mothers in the principles of infant care and welfare. No roentgenographic or clinical evidences of scurvy were encountered despite the frequent findings of very low concen-

trations of ascorbic acid in the blood samples from these children. Other studies, not as yet reported, indicated that the reserve stores of food substances had been greatly depleted. The authors concluded that the deprivations of important foods had not been going on for a long enough period of time nor had been great enough in amount to lead to clinical disease, but with continuation of unfavorable conditions for another year open manifestations of disease could be expected to become more and more frequent.

Despert^{15a} recently published a preliminary survey of children's reactions to the present war. In this review she carefully evaluated the psychiatric bibliography reports of the past few years, both foreign and American, and presented some personal observations on a group of New York children. The impression is gained from the British reports that the mass evacuation of 1,500,000 mothers, children and physically handicapped individuals from London early in the war resulted in widespread psychologic maladjustments and anxiety states. Most observers agreed that the harmful effects of evacuation were worse than the "raid-shock" of black-outs and bombings. The main source of difficulty was the separation of children, especially the younger ones, from their parents. In the absence of control data on symptoms existing prior to the war, it is difficult to properly evaluate the significance of behavior disturbances manifested by the children in the evacuation camps and foster homes. The most prevalent complaint was enuresis. Whether or not delinquency increased remains a moot point. An increase in restlessness and irritability especially in the pre-school age group was reported. Despert describes Brander's^{7a} contribution on evacuation and air-raids and their immediate and after-effects on Finnish children during the Russo-Finnish war of 1939-40. Agitation, claustrophobia, night terrors, stereotypies, tics and enuresis followed the bombings. Even when there were no bombings the continuous air-raid alarms gave rise to persistent tension and an insufficient amount of sleep, which caused the children to exhibit symptoms of nervousness. The children's reactions during raids were greatly influenced by the behavior of the people about them. Six months after the war Brander made an attempt to evaluate the reactions of the children to the war. He found that any stimulus which would recall the war elicited psychogenic reactions and neuropathic symptoms. War was reflected in the games of the children. Though there were very few cases of serious psychiatric disorders attributable to the war experience, he concluded that profound changes had taken place in the Finnish child's psychic life as a consequence. In Despert's observations on American children, in every case in which parents reported anxiety in relation to the war the child was found to have presented previously an anxiety problem. Children in the United States have not been subjected to the violent experiences of their European cousins nor do they exhibit symptoms of profound psychic trauma.

Medical Relief. Mackenzie³⁵ and others¹⁴ have been emphasizing the delay at the close of the last war in getting aid to the conquered countries with confusion and costly overlapping among the various relief organizations. To avoid a similar tragedy in the years to come, it is imperative that in the central administrative program for post-war reconstruction there be set up effective coordinating machinery for administering proper medical relief as promptly as feasible.

To the Reviewer it seems that opportunity should be provided within the relief organizations for the scientific investigation as well as treatment

of malnourished and disease-ridden childhood populations. From the study of such war-sick children can come a clearer understanding of the countless physiologic mechanisms at work within every child, and the relative effectiveness of various prophylactic, nutritive and curative agents in current professional use can be subjected to comparative analysis. If the supervision and practical management of medical relief for the childhood fraction of stricken people were entrusted to skilled pediatricians, not only would these children receive excellent attention but the clinical material could serve for the elucidation of lessons of significance for all children of the future.

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GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

FRANK B. BLOCK, M.D.

SURGEON, JEWISH HOSPITAL, PHILADELPHIA, PA.

AND

DOUGLAS P. MURPHY, M.D.

ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

NAUSEA AND VOMITING OF PREGNANCY

By MARY BENSON HALL, A.B.

The Scope of the Problem. During the first trimester of pregnancy about one-half to two-thirds of women experience some degree of nausea and vomiting. This can be considered severe, however, in only about one-third of the patients¹³ and necessitates hospitalization in approximately 1 out of 150 private patients.^{27,45} Among those attending clinics the incidence is considerably less, varying from 1 in 400⁴⁵ to 1 in 800.²⁷ In Denmark (population 3.7 million, 65,000 births annually) hyperemesis gravidarum accounts for about 6 deaths and 30 to 40 therapeutic abortions a year.⁴

Apparently neither color, age, race, parity nor marital status have any bearing on the occurrence of hyperemesis,^{16,40} although it is said to have an earlier onset and run a longer and more severe course in primiparas.²⁹ Fewer cases have been reported from Germany and England than from the United States and France,⁹ but hyperemesis is practically unknown in the Oriental countries with the exception of Japan. This occurs in spite of the fact that Oriental women live, according to our standards, under very unsanitary conditions, and exist on a diet which is deficient in vitamins A and B and calcium. Also, such conditions as cystitis, nephritis

and pyorrhea, which are frequently incriminated as foci of infection, are found much more commonly among these women than among those of the Occident.⁵⁸

It is generally agreed that hyperemesis complicates only the pregnancy of human beings. Numerous attempts, however, have been made to reproduce it in lower animals such as dogs and cats.^{20,37}

Clinical Picture. Although some authors⁴¹ state that three-fourths of patients begin to vomit before the first missed period, most clinicians consider that the usual onset is about the 6th week. The condition may last only a few weeks or extend over a period of 2 to 3 months,³⁴ but generally the woman is symptom-free^{9,13} by the beginning of the second trimester. The severity varies from a slight feeling of nausea on arising in the morning and distaste for food, to a condition of severe dehydration and emaciation and apparently toxemia.

The term "toxemia" should be employed with considerable caution because as yet no specific toxins have been isolated, although the clinical and pathologic findings resemble those seen in other toxic conditions.

Pathologic Anatomy. The kidney and liver in fatal cases show cloudy swelling and fatty degeneration; and in addition, centrilobular necrosis may be observed in the liver. Even the picture of acute yellow atrophy has been noted at times.¹² If these findings were confirmed, they would suggest that a toxin was the etiologic agent. Sheehan,⁴⁹ however, has been unable to do this. His only consistent finding was that hearts from patients dying of hyperemesis rarely weighed 230 gm.; whereas a heart of this small size was observed rarely in association with ordinary pregnancy. He also called attention to the many symmetrical, pin-point hemorrhages in the corpora mammillaria and thalami resembling those found in Wernicke's encephalopathy, Korsakoff's syndrome and in some other toxic states. In severe cases hemorrhages are noted in the retina.^{60,65}

Unfortunately the postmortem findings cannot be taken as conclusive evidence of the presence of a toxin, because they can be explained also on the basis of the cycle of vomiting-dehydration-emaciation-inanition-starvation, once such a cycle is initiated by some factor associated with the pregnant state.^{10,49}

The etiologic theories fall into two main groups, the neurogenic and the organic.

Neurogenic Theory. Practically everyone admits the presence of a neurogenic factor; first, because the disease is more prevalent among those women with more leisure time, and among those who, before pregnancy, were regarded as somewhat unstable psychically^{4,48} (*a priori* reasoning, perhaps); and second, on account of the excellent response of the condition to psychotherapeutic measures such as isolation and positive suggestion. Atlee³ has reported on 33 patients whose hyperemesis was handled as a purely neurotic manifestation. Only 4 women failed to respond to this treatment. Two of these (unmarried girls) died of intercurrent pneumonia. The other 2 were aborted therapeutically, and although their fetuses were not actually expelled until 2 days later, vomiting ceased as soon as the patients believed that their pregnancies were terminated. One of these last 2 women responded to psychotherapy for hyperemesis in a subsequent pregnancy.

Atlee's interpretation of hyperemesis is as follows:

Vomiting of pregnancy is a protest against pregnancy on the part of the unconscious mind—a defense or rejection tendency, directed against what is unconsciously felt as a foreign body, but displaced (in the psychological sense) and carried out

in regard to the gastric contents. Only in the second half of pregnancy, when the movements of the child no longer permit even the hysterical woman to deny the genital location of the changes and sensations, does the inclination to vomiting cease . . . vomiting is a distorted attempt on the part of the unconscious mind to rid the self of the fetus.

To account for the pathologic findings Atlee submits the following points: (1) Laboratory animals dying from starvation or continued loss of gastric juice present the same pictures in their livers as the woman dying from hyperemesis. (2) Starvation sensitizes the liver to poisons. Mental fatigue, undernourishment and use of salvarsan in Germany during the years 1916-20 were associated with an increase in acute yellow atrophy. (3) Mental disturbances *per se* can produce hepatic changes indistinguishable postmortem from those seen in fatal cases of hyperemesis gravidarum. (Cases cited.)

Another reason, advanced in support of the neurogenic theory, is the occurrence of vomiting and similar symptoms among the husbands of pregnant women.³ Most authorities, however, think the incidence of this phenomenon is too small to be conclusive.⁵⁹

The opponents of the neurogenic theory point out that the majority of women cannot be regarded as psychotic, yet when pregnant the majority do suffer from some degree of vomiting.²⁸ Moreover vomiting may have its onset before the first missed period or before the woman suspects that she is pregnant.⁴⁴ The tendency here is to regard the neurosis as an aggravating factor and very likely one which obscures the true cause.^{12,19,30,38,44,64}

Organic Theories. 1. *Those of Paternal Origin.* Aside from his influence on the mental outlook of the woman, the father is incriminated as being responsible for hyperemesis only by the appearance, *via* the fetus, of isoagglutinins in the mother's blood, a mechanism similar to that of the Rh antigen in causing erythroblastosis fetalis.^{25,33} This, however, has been proven in only a few cases, and some investigators²⁵ have even used injections of father's blood to bring an end to vomiting, but their success probably may be ascribed to a non-specific psychotherapeutic effect.

2. *Those of Placental Origin.* Many theories center around a derangement of the placenta as the etiologic agent. One group of French workers⁴ believes that pathologic changes in the chorionic villi are responsible for the vomiting. To support this theory these investigators cite cases similar to the following 2: A woman died 14 days after the onset of hyperemesis. She was found to have a hydatidiform mole, the normal course of which is more than 1 month. Another woman who continued to vomit for 26 days after abortion was subsequently shown to have retained a fragment of placental tissue. Ordinarily recovery should occur within 2 weeks at most. There are, however, many such patients who do not suffer from vomiting or any other toxic signs. Obviously, then, some other factor must be at work.

This may be fragments of chorionic villi and detached masses of chorionic epithelium which are found often within the maternal blood-vessels. Peckham⁴⁴ postulates that the normal mother can dispose of such foreign bits of tissue satisfactorily, but when the nervous system is upset, as during pregnancy, she is unable to do this—a point difficult to prove.

Another theory is that of Johnson,²⁶ who says that stasis of blood in the intervillous spaces, if of sufficient duration, leads to degeneration of chorionic tissue and the production of tyrosine. Bacteria and/or enzymes circulating in the blood convert tyrosine to tyramine, and the absorption of the latter is responsible for the symptoms of hyperemesis.

Viet and others^{54,63} postulate the presence of a syncytiotoxin, whose source is the placenta, a toxin normally neutralized by a substance called syncytiolysine. For some reason the mechanism fails, and the mother is no longer able to destroy the fragments of villi which are circulating through her body. The symptoms of hyperemesis are produced by the direct action of the toxin on the vomiting center and the vital organs.^{20,48} In support of this theory is the evidence that urine from a toxemic gravida must be diluted considerably before it can be injected safely into mice for the Aschheim-Zondek test.⁹ Clinically the eye manifestations, *i. e.*, nystagmus and retinal hemorrhage, resemble those found in other toxic conditions.^{8,60} There is also a marked similarity of the symptoms of severe hyperemesis to those of the toxic psychoses⁶ and of mild cases to the so-called toxemia of amenorrhea.¹¹ Nevertheless, it still remains for this toxin to be isolated and its source determined.

3. *Those of Maternal Origin.* (a) Intercurrent Processes: Vomiting may, of course, be produced in the pregnant woman by any condition which causes the non-pregnant woman to vomit. Such would include tonsillitis,⁹ gastritis,⁹ appendicitis,⁹ cervicitis,^{9,52} cholecystitis,⁵² peptic ulcer,⁵² nephritis,¹¹ urinary back pressure,²² the presence of tapeworms,⁴² as well as innumerable other causes. Pyelitis,^{9,41} hyperthyroidism¹⁶ and avitaminosis^{35,36} also will cause vomiting. These three conditions are associated more commonly with pregnancy than the preceding ones, and if they are present in a more or less latent state before pregnancy, the extra demands of the fetus will be apt to make them worse.

A word should be said in regard to avitaminosis-B. Since some of the neurologic signs found in severe cases of hyperemesis resemble those of polyneuritis and Korsakoff's syndrome, the B complex has been thought to play an important rôle in the development of vomiting.⁵⁶ Likewise the convulsions, which may be associated with hyperemesis gravidarum but which are seen more commonly in eclampsia, may be correlated with low pyruvic acid levels.³⁵

(b) Metabolic Derangements: Theories in support of a basic metabolic derangement as the cause of hyperemesis center about the liver for three reasons: (1) Postmortem changes are most marked in the liver. (2) Hepatic function tests (porphyrin and bilirubin elimination, the xanthoproteic test)^{23,46} indicate decreased activity. (3) Examination of the blood and urine reveals disturbances of body metabolism associated with hepatic damage.

These biochemical findings^{44,45,54,62,65} include increased blood urea nitrogen, acetone bodies, and blood organic acids (uric, amino and lactic) and decreased blood chlorides. The CO₂ combining power varies widely but is generally within normal limits. The van den Bergh test is slightly positive in moderately severe cases. Serum proteins, hemoglobin and red blood cell counts are high as a result of the dehydration and hemoconcentration. The blood sugar usually is depressed, although in severe cases increased values are sometimes found.⁴⁴ The urine is loaded with albumin, acetone bodies, and the products of bile pigment metabolism. The ammonia nitrogen coefficient is increased, and this Peckham⁴⁴ attributes to starvation.

The glycogen reserve of the liver¹⁹ is decreased either through prolonged fetal demands—at this time the placenta, the great storehouse, is not completely formed⁶⁴—or because the dietetic habits and preferences of the mother result in a decreased carbohydrate intake.⁶² Such a prolonged, gradually increasing hypoglycemia may give rise to neurotic symptoms⁶²

and will sensitize the liver to the action of toxins. Experimentally it has been shown that less poison is required to kill an animal whose liver has been depleted of its carbohydrate reserve than to kill a normal one.⁶¹ Once vomiting has begun a vicious circle is set up, for continued vomiting further depletes liver glycogen. The intravenous administration of glucose to combat this loss will, in many cases, restore the woman to health⁶² and is a fundamental part in the treatment of these patients.

The effects of a deranged carbohydrate metabolism are felt also on other reactions of the body. Sussman⁵⁷ has pointed out that the normal response of the body to parathormone is decreased greatly in the presence of liver damage. Ordinarily calcium will relieve the symptoms of CCl_4 , phosphorus and hydrazine poisoning whether hypocalcemia is demonstrable or not. A patient with hyperemesis, however, does not cease vomiting when calcium is administered alone, but she will obtain relief if parathormone is given in addition to the calcium.

The ketosis, acidosis and shift in pH observed in these women is linked also to the question of deranged carbohydrate metabolism.⁴⁴ In dogs, a disturbance in acid-base equilibrium unassociated with renal injury has been found to produce a toxemic condition.³⁷

It is possible that the metabolic disturbance can be explained on the basis of the next topic to be considered.⁴³

(c) Endocrine Dysfunctions: Due to the rapid development of the endocrine system during the first trimester of pregnancy, almost all of its hormones have been held responsible for hyperemesis. The following are some of the important ones:

Gonadotropin: During pregnancy the anterior pituitary gland increases in size, and from the chromophobe cells new ones develop. These contain acidophilic granules and are known as "pregnancy cells."⁵ It is not unreasonable to assume, therefore, that the gonadotropic hormones, as well as those which exert a trophic effect on the other endocrine glands such as the thyroid, adrenal and parathyroid, increase in amount.

Numerous workers have attempted to demonstrate an hyperprolancinia and hyperprolanuria in association with hyperemesis. Data published between 1936 and 1939^{7,20,32,47} suggested that the amounts of gonadotropic hormone in the blood of patients suffering from hyperemesis were greater than those present in normal pregnancy. One group of investigators⁷ thought that it was able to correlate the level of prolan with an abnormal proliferation of plasmodial elements in the placenta, but subsequent workers^{4,53} have not been able to confirm these observations.

Estrogen: Determinations of the amounts of the estrogens in the blood and urine have shown that nausea is associated with low estrin levels.⁵¹ and Hawkinson^{20,21} has reported both low estrogen and high gonadotropin values in such patients. Over 150 of these women were treated successfully with estrogenic preparations. Nevertheless synthetic estrogens can themselves produce nausea and vomiting.¹⁸ Smith and Smith^{9,50} postulate an abnormal metabolism of estrogens at this time of such a degree that there is an excessive destruction of them.

Anterior Pituitary-like Substance: Subnormal urinary values for APL associated with hypernormal values in the serum have been reported from a small series of cases by some Norwegian workers.⁷ These values returned to normal following recovery from vomiting.

Adrenocortical Hormones: One theory attributes nausea and vomiting to adrenocortical failure. The evidence in support of this view is:^{4,29}

- (1) Normally the adrenal cortex hypertrophies during pregnancy, but in fatal cases of hyperemesis, it is found to be atrophic.
- (2) Nausea and vomiting are the first symptoms in adrenalectomized animals.
- (3) Anorexia, nausea and vomiting are the first symptoms of Addison's disease.
- (4) Biochemical findings in hyperemesis and Addison's disease are similar.
- (5) Treatment with adrenocortical extracts will terminate vomiting.

In comment on this last point, it should be pointed out again that the therapeutic effects are very difficult to evaluate because of the strong susceptibility of the condition to psychotherapy. Bandstrup⁴ says, "When an effect is obtained it seems reasonable to look upon it as a palliative and compensatory (measure) through increase in the liver glycogen and blood cholesterol, that is, a treatment along the line of the glucose-insulin treatment."

Interfunction of Adrenal and Pituitary Glands: Elevation of blood cholesterol, a common finding in hyperemesis,^{55,63} suggests a disturbance of fat metabolism, the controlling agent of which is considered to be the ketogenic hormone of the anterior pituitary gland. Cholesterol is said to counteract this secretion and also to neutralize both endogenous and exogenous toxins and to increase liver glycogen.^{53,63} Kemp²⁸ suggests that the liver can function efficiently and maximally only in the presence of an adequate catalyst and proposes that this may be an adrenocortical secretion.

(d) Allergy: The rôle of allergy in the production of nausea and vomiting is closely linked with that of the endocrine glands, for the causative agent is considered to be the corpus luteum hormone. There are those⁴³ who contend that an excess of corpus luteum hormone secreted at the time of conception may be responsible for hyperemesis but the chief reason advanced is that the woman has become sensitized to the corpus luteum hormone through continued absorption during her active sex life. Vomiting appears at the time when corpus luteum is increasing physiologically in size, and stops when the corpus luteum ceases to grow.^{24,54} (The proponents of this view point out that the corpora lutei of the pregnant and the non-pregnant woman may not actually be the same, for on microscopic section those of the latter contain more colloid and larger granular cells.) Finch^{13,14,15} was able to demonstrate in a large, well-controlled series of patients positive intradermal reaction to an extract of the corpus luteum (not progesterone but an as yet unidentified hormone), proportional in almost every case to the degree of nausea and vomiting the patient experienced. He has found also that patients who have had nausea and vomiting during pregnancy are extremely likely to experience it following the administration of diethylstilbesterol for any other clinical condition for which it may be indicated. These patients all show positive intradermal tests with the corpus luteum hormone. From this he infers that the allergen very likely is some substance produced secondarily by an estrogenic substance such as diethylstilbesterol. Furthermore, desensitization can control the patient's symptoms.

(e) Miscellaneous Conditions: In addition to the causes given above, there are a number of others which have been proposed but whose rôle in the production of hyperemesis has not as yet been thoroughly investigated. These include hunger,⁵⁴ duodenal spasm,³⁹ faulty protein digestion,^{52,54} achlorhydria,^{2,20} reverse peristalsis brought about by hyperemia and growth of pelvic structures,²⁰ unstable nitrogen equilibrium^{31,34,43} and overirritability of the vagus.⁵⁴

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 20, 1943

Studies on Gelatin as a Plasma Substitute. I. Efficacy of Gelatin in Experimental Hemorrhage and Burn Shock. W. M. PARKINS and J. S. LOCKWOOD (Harrison Department of Surgical Research, University of Pennsylvania). The gelatin used in these studies was produced by alkali hydrolysis of bovine long-bone collagen under controlled and standardized conditions, and was infused as a 6% solution in saline, having a colloid osmotic pressure, after autoclaving, of about 45 mm. of Hg.

Ten unanesthetized dogs subjected to rapid massive hemorrhage to the point of air hunger or respiratory failure, with blood pressure reduced to about 20 mm. of Hg, all survived when immediately infused with a volume of saline or gelatin equivalent to the amount of blood withdrawn (approximately one-half their blood volume). The maintenance of a higher total protein concentration in the 5 gelatin infused dogs, the considerably greater increase in plasma volume, and the return of the blood pressure to normal range 15 minutes after infusion, in contrast to the response of animals to saline, indicates a definite superiority of gelatin over saline in this type of experimental hemorrhage.

Dogs anesthetized with nembutal, subjected to hemorrhage of 30 cc. per kg., and infused with gelatin were better able to tolerate subsequent repeated hemorrhages of this amount than animals infused after each hemorrhage with saline.

Sixteen dogs under nembutal were subjected to a standard procedure of slow 3-stage hemorrhage with blood pressure maintained at 30 to 40 mm. Hg for 30 to 40 minutes. Three untreated animals succumbed within 2 to 5 hours. Two of 5 saline-infused animals slowly recovered and 3 died within 6 hours. In 5 gelatin-infused animals the increase in plasma volume was more marked than in 3 plasma-infused dogs. In the gelatin-infused dogs the blood pressure was as well restored and maintained as in the animals receiving plasma. All gelatin and plasma-infused dogs made a rapid and uneventful recovery.

Treatment of anesthetized dogs subjected to a standard reproducible body burn yielded the following results: All of 5 control animals died; 3 of 5 saline-treated animals succumbed with uncontrolled hemoconcentration; 1 of 4 plasma-treated dogs died, and 7 of 8 gelatin-treated dogs failed to survive in spite of a correction of hemoconcentration of the same degree as that obtained with plasma. Although gelatin treatment extended survival well beyond the period when death associated with hemoconcentration occurred in controls, the gelatin-treated dogs showed a progressive decline in blood pressure without significant reconcentration. Since gelatin is capable of compensating for the osmotic pressure of the lost plasma protein, there is reason to expect that the effectiveness of gelatin therapy in burns may be enhanced by modifying the composition and technique of administration of gelatin, and by the concomitant administration of certain humoral factors.

II. Observations on Toxicity and Elimination of Gelatin. C. E. KOOP, CECILIA RIEGEL, H. M. VARS, H. L. RATCLIFFE, W. M. PARKINS and

J. S. LOCKWOOD (Harrison Department of Surgical Research and Department of Pathology, University of Pennsylvania). Studies on the toxicity of intravenous gelatin as a plasma substitute were undertaken after single and repeated infusions of 10 to 30 cc. per kg. of 6% gelatin solution.

Glucose tolerance, serum protein, albumin and globulin, non-protein nitrogen, and prothrombin determinations revealed no liver damage. Fibrinogen levels were decreased. Bromsulfalein retention was marked 3 hours after infusion, diminished at 24 hours, and normal at 48 hours. The degree of retention became increased and the return to normal increasingly delayed as the number of weekly infusions increased. Similar but less marked retention was observed in dogs infused with plasma.

Kidney function as determined by urea clearance was unimpaired.

There is no evidence that gelatin *per se* is pyrogenic in the dog. Repeated infusions varying in amount, number and frequency failed to produce allergic reactions.

Sedimentation rates, corrected for hematocrit changes, showed a two- to fourfold increase after infusion, with return to normal as the gelatin disappeared from the blood.

Clotting time was increased 16% 15 minutes after the start of infusion, 30% at 3 hours, and returned to normal within 24 to 48 hours.

Following gelatin infusion diuresis and relatively rapid excretion of gelatin occurred which decreased after 6 hours following infusion. Not all of the gelatin which disappeared from the blood was accounted for by urinary excretion. The fate of the remainder is obscure. Plasma proteins fall rapidly after infusion and were replaced at about the same rate at which gelatin disappeared from the blood. Gelatin was present in only minute quantities after 5 days. A decrease in total plasma protein concentration which occurred soon after infusion may be explained by increase in plasma colloid osmotic pressure.

In the normal dog, repeated infusions of gelatin over long periods of time were not accompanied by demonstrable tissue damage, except for capillary hemorrhages in the adrenal glands which were visible for only 48 hours after the infusion. In those animals where gelatin was given as a blood replacement there was evidence of protein leakage in the kidney tubules and minor degeneration in liver and kidney in 24 hours. These changes, only slightly more marked with gelatin than with plasma, were apparently reversible.

Further Studies on the Mode of Action of Sulfonamides. M. G. SEVAG, JANE HENRY and RUTH RICHARDSON (Department of Bacteriology, University of Pennsylvania). The results of our studies show that proteins compete with bacterial enzyme proteins for sulfonamides, *i. g.*, neopeptone reverses the inhibition of the respiration of bacteria by sulfonamides. The reversing effect of neopeptone, contrary to Lockwood's postulates, is not due to acceleration of the metabolic activities of bacteria but due to a competition with bacterial enzymes for sulfonamides. This competition is effective when the amount of neopeptone is in excess of the amount required for optimal acceleration of the metabolic activities of bacteria. Similar competitive effects are observed also when the inhibition of the carboxylase activity of *E. coli* by para-, meta- and ortho-aminobenzene-sulfonamides are measured in the presence and absence of proteins. In the absence of proteins the 3 isomers exercise similar inhibitory effects. On the other hand in the presence of an appropriate amount of neopeptone

or human serum albumin, the para-isomer maintains its inhibitory effect, but the meta- and ortho-isomers show no inhibitory effect. The latter 2 isomers show, therefore, greater affinity for these serum proteins than for the bacterial enzyme proteins involved. p-Aminobenzoic acid reverses the inhibition of the respiration of bacteria by sulfonamides (50% to 100% reversal). p-ABA likewise reverses the inhibition of bacterial carboxylases by sulfathiazole. These and other facts show that the action of sulfonamides is directly related to the blocking of the respiratory enzymes of bacteria. (Sevag, M. G., and Shelburne, M., *J. Bacteriol.*, 43, 411, 421, 447, 1942; Sevag, M. G., Shelburne, M., and Mudd, S., *J. Gen. Physiol.*, 25, 805, 1942.)

Clinical Studies on Incoördination of the Circulation. ISAAC STARR (Research Department of Therapeutics, University of Pennsylvania). The change in the circulation when the subject arose, as determined by the ballistocardiograph, has been employed as a test of circulatory coördination; *i. e.*, of the ability to adapt its volume to the needs of the moment.

Normal standards were determined by a statistical analysis of the results of 120 tests made on 75 normal subjects. Abnormalities were sought in 200 tests made on 150 ambulatory hospital patients.

In healthy persons the amount of the circulation per minute changes but little when they arise. In a large percentage of sick persons the circulation, on arising, changes much more than in healthy persons. In the common abnormality the circulation after arising is unduly increased; in the far rarer type it is unduly diminished.

Incoördination of the circulation is a very common clinical condition and this may account for the widespread occurrence of symptoms such as dizziness, faintness and shortness of breath, which so many of these patients exhibit.

BOOK REVIEWS AND NOTICES

THE EMBRYOLOGICAL TREATISES OF HIERONYMUS FABRICIUS OF AQUAPENDENTE. THE FORMATION OF THE EGG AND OF THE CHICK. THE FORMED FETUS. A facsimile edition, with an introduction, a translation, and a commentary by HOWARD B. ADELMANN, Professor of Histology and Embryology, Cornell University. Pp. 883; 85 figs. Ithaca, N. Y.: Cornell University Press, 1942. Price, \$12.00.

THE translation of these two important embryological treatises—apparently for the first time in any modern tongue—and their facsimile reproduction from the most reliable editions constitute a noteworthy event in medical historical achievement in this country. Further value is added by the 121 pages of the scholarly preliminary matter on the “colorful” life of Fabricius and the history of embryology before Fabricius’ time, together with an analysis of the two embryological treatises, and inclusion of the unique supplement of 10 leaves of explanatory matter accompanying the colored plates bound in the copy of *De Formato Foetu* that is in the Library of the College of Physicians of Philadelphia. The spelling of Fabricius’ birthplace without the “c” in the title and with it in some places, as on page 6, merely reflects the frequent variation that is found on this point. A similar explanation must serve for the confusion about dates of printing *De Formato Foetu*. The author explains (p. 122) the different dates used in title page, colophon and dedication and his reasons for preferring the 1604 of the colophon.

To the tyro in medical history the name of Fabricius perhaps first recalls three items: his construction of what was perhaps the first permanent anatomic theatre, in Padua, and his chief contributions to medical progress—the recognition of the valves of the veins and as the teacher of Harvey at Padua. His influence as a teacher and investigator was undoubtedly an important factor in stimulating his more brilliant pupil toward his synthesis of the circulation of the blood: Less well known, however, are these embryological treatises, which also stimulated Harvey, by his own acknowledgment, to the construction of his second great work. Dr. Adelman’s evaluation of Fabricius’ contribution steers a middle course between the extremists who see in Fabricius anything from the leading figure in a period full of leaders, on the one hand, to a traditionalist “blinded to facts staring him in the face” (Foster). Rather does Adelman look on Fabricius the embryologist as a strong and intelligent observer and pictographer, a proponent of useful classifications and tools of expression; but one who, as a child of his times—such as Harvey himself was—bowed occasionally too low to authority and to the dead hand of Galen. Fabricius, of course, made errors of observation and interpretation, some of which were picked up by his pupil, Harvey, who in turn made the same sort of errors. But how could anything else be expected, given the complexity of the subject, the fragmentary basis of the scientific knowledge of the day, and the lack of suitable instruments permitting more precise study? He should be regarded as a follower of Aristotle only partly freed from the fetters of omnipotent tradition. Fabricius’ position among the great in anatomy and embryology is clarified and enhanced by Adelman’s work.

Hearty congratulations are in order to the American Council of Learned Societies for aiding financially in the publication of the volume, to the Cornell University Press for the excellent, and yet not over luxurious format, and above all to a busy Professor of Anatomy and Embryology whose enthusiasm for books and their contents enables him to bring his task to a successful completion in these difficult times.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 27, No. 1, Chicago Number, January, 1943. Pp. 267; illus. Philadelphia: W. B. Saunders Company, 1943. Price, year \$6.00.

MORE than once Sir William Osler, suggesting the way to Aequanimitas, indicated that physicians would do well to compose themselves for sleep by perusing volumes far from the field of medicine. That advice gently put forth, in more leisurely days of course, can stand the test of time; but in these strained days, when physicians practising general medicine must be rationed and their time packed with consultations to the exclusion of their regular medical reading, this number of the *Medical Clinics of North America* will be welcomed by them. It has proved to be a stimulating bedside companion to be read profitably, perhaps an article at a time, without unduly exciting the resting physician.

The present number is chiefly devoted to gynecologic problems, but, as usual, includes other topics, chiefly on diagnosis and treatment. V. R.

DISEASES OF THE SKIN. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology, University of Illinois; Attending Dermatologist to the Presbyterian Hospital of Chicago; etc.; and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research Graduate School, University of Minnesota, Rochester, Minn.; etc. Pp. 1360; 654 figs. (6 colored plates). Sixth ed. Philadelphia: Lea & Febiger, 1943. Price, \$14.00.

IN this edition, long a most distinguished example of the best American tradition in the field, Dr. Ormsby is again fortunate in the choice of his collaborator. Dr. Hamilton Montgomery, of the Section of Dermatology and Syphilology of the Mayo Clinic, is an able clinician and competent pathologist. He has, singly or in collaboration, made intensive studies on a number of the complex phases of dermatology. His collaboration with Dr. Ormsby is especially evident in the section on the diseases of metabolism (xanthoma) and in his additions to the paragraphs on pathology which the previous collaborator, Dr. W. C. Finnerud, had revised in the two preceding editions.

The authors have added descriptions of 22 diseases not previously dealt with in the text. The illustrations are generally good but some represent far from typical examples of the dermatosis under consideration.

The text is concise, systematic and up-to-date. The reader is supplied with adequate recent bibliography as well as with some of the classic references.

There are but few adverse criticisms one can make of this book. The section on syphilis, however, is somewhat weak, and, except for the dermatologic aspects, cannot be regarded as adequate for a full understanding of the disease. Certain minor errors, such as placing a discussion of sobisminol (page 960), a bismuth preparation for oral use, in the section on mercury, are inevitable in so large a book as this.

The Reviewer believes that Ormsby and Montgomery's revision of Ormsby's *Diseases of the Skin* is to be highly recommended for medical students and practitioners. H. B.

THE BIOLOGICAL ACTION OF THE VITAMINS. A Symposium. Edited by E. A. EVANS, JR., Associate Professor of Biochemistry, The University of Chicago. Pp. 227. Chicago: The University of Chicago Press, 1942. Price, \$3.00.

IN connection with the Fiftieth Anniversary Celebration of the University of Chicago, the Universities of Wisconsin and of Chicago arranged a symposium on the vitamins. One group of papers was presented at meetings held in Madison, Wis., and has been published under the title "The Respiratory Enzymes." The present volume includes the papers presented at the Chicago meeting. Following a general discussion of the title topic by C. A. Elvehjem,

there are stimulating discussions of a number of the vitamins by the foremost chemists, physiologists and clinicians working in this field. While all the papers are noteworthy, 3 are of special interest to those who have followed the progress of research in vitamin chemistry and physiology: the *Biotin* story related by du Vigneaud; *Choline*, by Wendell H. Griffith; and, *The Economy of Phosphorus in the Animal Organism*, by Franklin C. McLean. E. W.

CHEMOTHERAPY OF GONOCOCCIC INFECTIONS. By RUSSELL D. HERROLD, B.S., M.D. Pp. 140; a few tables. St. Louis: C. V. Mosby Company, 1943. Price, \$3.00.

THE author presents a much needed volume on a subject of great importance, especially in wartime. The treatment with sulfonamides has opened a new era in the handling of gonorrheal patients. Since the introduction of sulfanilamide in 1935, the literature has contained many reports on the effects of individual sulfonamides on small isolated groups of patients. By necessity, such reports are of importance in the early evaluation of the drugs as they are presented. Herrold presents an experience derived from observing many hundreds of patients treated with various substances. He covers all phases of the approach and method of therapy of gonorrhea with sulfonamides.

The book is complete and readable. It should be available to all physicians treating gonorrhea. L. LaT.

THE FOOD YOU EAT: A PRACTICAL GUIDE FOR HOME NUTRITION. By SAMUEL GLASSTONE, Professor of Chemistry, University of Oklahoma, and VIOLETTE GLASSTONE, University of Oklahoma, Norman, Okla. Pp. 277; 18 illus. Norman, Okla.: University of Oklahoma Press, 1943. Price, \$2.25.

BECAUSE perhaps of the wartime shortages and rationing of foods, public interest in this subject and its relation to good health has been greatly accelerated. This book is therefore appropriate at this time and gives the intelligent layman a readable account of the complex subject of nutrition, digestion, and the preparation of foods. Approximately the first half of its contents is devoted to the physiology of metabolism and food requirements, while the remainder is devoted to a discussion and evaluation of food products and the menu. The Reviewer believes that this book will find a useful place in the home of the concerned housewife; likewise, it answers many of the common food questions received by the practising physician. D. T.

CLINICAL LABORATORY DIAGNOSIS. By SAMUEL A. LEVINSON, M.S., M.D., Director of Laboratories and Pathologist, Research and Educational Hospitals, Chicago; Professor of Pathology and Assistant Professor of Medicine, University of Illinois College of Medicine; and ROBERT P. MACFATE, Ch.E., M.S., Ph.D., Assistant Director of Laboratories, Research and Educational Hospitals, Chicago; Assistant Professor of Pathology, University of Illinois College of Medicine. Second ed. Pp. 980; 156 illus., 15 plates (7 in color). Philadelphia: Lea & Febiger, 1943. Price, \$10.00.

RETAINING their objective of a laboratory text which is relatively comprehensive and yet concise, practical, usable, and arranged to make the facts easily accessible, the authors have brought all data and procedures up to date. Many of the newer procedures, such as those for the Rh factor, sulfonamides and phosphatase, have been added, and the text has been enlarged and certain non-essential portions deleted. This volume remains, in the Reviewer's opinion, one of the best in print, triply as a text for students, quick reference book for practitioners, and laboratory manual for technicians and clinical pathologists. M. F.

ANNUAL REVIEW OF BIOCHEMISTRY, VOL. XI. Edited by JAMES MURRAY LUCK. Pp. 736. California: Stanford University, 1943. Price, \$5.00.

THIS review is along the same general lines as the previous volumes. Many of the same subjects are reviewed such as chemistry and metabolism of carbohydrates, fats and proteins. There are the usual two chapters on vitamins, one on biologic oxidations and reductions, one on hormones, and so forth. As usual, a few subjects less frequently reviewed or reviewed for the first time have been included. Among these may be mentioned the chapters on The Chemistry of Visual Substances, Avian Biochemistry and Plant Tissue Cultures. In spite of the war several foreign authors have contributed to this review and the usual high standard has been maintained. J. J.

PSYCHOLOGY YOU CAN USE. By WILLIAM H. ROBERTS. Diagrams by JAMES MACDONALD. Pp. 246. New York: Harcourt, Brace & Co., 1943. Price, \$2.00.

THE extremely simple, almost monosyllabic language in which this book is written goes a long way toward accomplishing the purpose for which it was written. Fundamentally, it is a semiscientific introduction, for the layman, of the *science* of psychology. The popular conception of psychology as being a study in "How to Win Friends and Influence People" is exploded. Instead, the author gives clear, definite concepts of the importance of this science; why and how concrete reactions and stimuli affect the body and the mind and make the individual react as he does. It is the explanation of behavior and experience in a physical environment—much as a plant is studied in its physical surroundings, or any other living organism.

This book can be recommended to the general lay public as a simple, scientific explanation of a science that still is clouded with a lot of fancy mysticism. E. F.

ENDOSCOPIC PROSTATIC SURGERY. By ROGER W. BARNES, M.S., M.D., F.A.C.S., Professor of Clinical Urology, College of Medical Evangelists; Chief of Urology Service, White Memorial Hospital and Out-Patient Clinic; Senior Attending Surgeon, Los Angeles County Hospital. Pp. 235; 104 illus. St. Louis: C. V. Mosby Company, 1943. Price, \$6.00.

THIS contribution is a much needed treatise on endoscopic prostatic surgery. The information presented could be obtained only by an exhaustive review of the literature, as well as wide personal experience.

Anyone having done endoscopic prostatic surgery realizes that the technique is not one that can be mastered by the study of any book. However, much trouble may possibly be avoided by following the suggestions that Dr. Barnes presents. This book should be available to every student of urologic surgery, as well as to those who have any part in the care of prostatic patients. L. LaT.

THE PRINCIPLES AND PRACTICE OF WAR SURGERY WITH REFERENCE TO THE BIOLOGICAL METHOD OF THE TREATMENT OF WAR WOUNDS AND FRACTURES. By J. TRUETA, M.D., Formerly Director of Surgery, General Hospital of Catalonia, University of Barcelona; Assistant Surgeon (E.M.S.), Wingfield-Morris Orthopaedic Hospital, Oxford; Acting Surgeon-in-charge, Accident Service, Radcliffe Infirmary, Oxford. Introduction by OWEN H. WANGENSTEEN, M.D. Pp. 441; 144 illus. St. Louis: The C. V. Mosby Company, 1943. Price, \$6.50.

THE author's extensive experience in the Spanish Civil War has given him definite and enthusiastic opinions regarding the value of the closed plaster method of treatment for compound fractures. He has adapted and modified

this method, which has been most widely known in this country as the Orr method, for use in many types of injury.

The book is quite didactic and very readable. Some readers may be unable to agree with certain of the statements on physiological and biochemical subjects; for instance, "Blood pressure is the essential factor in the intensity of shock, and everything else must be related to it" (p. 133), or the statement in regard to burns, "Glycogen is often given off by the liver producing hyperglycemia and acidosis"

The book is absorbing to read and presents a large amount of most valuable clinical experience. The fact that it is based on experience gained in the management of the casualties of modern warfare would seem to make it of great practical value today.

J. R.

AN INTRODUCTION TO BIOPHYSICS. By OTTO STUHLMAN, JR., Ph.D., Professor of Physics, University of North Carolina. Pp. 375; many figs. and tables. New York: John Wiley & Sons, Inc., 1943. Price, \$4.00.

THIS book is intended to meet "the increased demands for physics by students whose primary interests lie in the biological sciences." The principal topics covered include Roentgen rays, radio-activity, biologically active light, vision, auditory mechanisms, structure and properties of surfaces and membranes, and nerve conduction.

The physics discussed largely concerns the instruments and methods employed rather than the physical analysis of the properties of the biologic systems themselves. There is an extensive discussion of the physics of various kinds of radiations including artificial radio-activity. The optical system of the eye and mechanics of sound transmission in the ear are discussed. There is a chapter on the compound microscope and the electron microscope including the formulas for magnetic and electric focusing of electron beams. There is also an analytical consideration of electron deflection in the cathode-ray oscillograph. A generous bibliography is provided for each chapter, and a series of problems offered at the end of the book.

M. L.

BIOCHEMISTRY AND MORPHOGENESIS. By JOSEPH NEEDHAM, F.R.S., Sir William Dunn Reader in Biochemistry, and Fellow of Gonville and Caius College, Cambridge. Pp. 785; 328 illus. (4 of which in color). Cambridge: The University Press. New York: The Macmillan Company, 1942. Price, \$12.50.

THIS volume follows the author's "Chemical Embryology" (1931), in which the chemical changes going on during embryonic development were presented. Since then a new approach to the problem of morphologic-chemical relationship has developed: namely, an investigation of morphogenetic substances. It is with this subject that the present work is concerned.

The existence of these substances was revealed in the work of Ross Harrison, Warren Lewis, Hans Spemann, and Otto and Hilde Mangold. Since then, attempts to isolate the induction factors has progressed. The book is a stimulating one, written in a clear and understandable manner. Whereas the subject is still filled with irritating gaps in our knowledge, the general pattern of morphogenesis and its chemical background emerges more and more clearly. The work is of importance to everyone interested in the biologic sciences. Its material is significant not only for the biochemist and embryologist, but also for the physiologist and pathologist; it comes as a fresh breeze to subjects somewhat overburdened with purely descriptive morphology. Furthermore, it serves as an introduction to the probable future course of development of the biologic sciences.

The volume is divided into three parts. In Part I the morphogenetic substratum is considered, including such subjects as the constitution of the eggs

of invertebrates and vertebrates, environmental factors and embryonic nutrition. In Part II, the major part of the book, the general concepts of morphogenetic stimulation are presented. Organizers and their specific functions are fully dealt with, as well as the relation of organizers to genes. An interesting discussion of the possible rôle of organizers in carcinogenesis is included. In Part III, the morphogenetic mechanisms are considered: dissociability, heterauxesis, respiration, metabolism and polarity.

D. C.

PROTEINS, AMINO ACIDS AND PEPTIDES as IONS and Dipolar Ions. By EDWIN J. COHN and JOHN T. EDSALL, Harvard Medical School. Including Chapters by JOHN G. KIRKWOOD, Cornell University, HANS MUELLER, Massachusetts Institute of Technology, J. L. ONCLEY, Harvard Medical School, GEORGE SCATCHARD, Massachusetts Institute of Technology. Pp. 686; many tables and figs. New York: Reinhold Publishing Corp., 1943. Price, \$13.50.

THIS American Chemical Society Monograph, prepared by such well-known investigators, is a most welcome evaluation of the evidence concerning the size and shape of the molecules of amino acids, peptides and proteins and the number and distribution of the electric charges they bear. The implications considered are of the effect of their charged structure upon their physical properties and their physico-chemical interaction with other molecules.

The fundamental studies of Debye and Hückel, and of Bjerrum serve as the basis for the approach to protein chemistry which is adopted here. From the data collected upon the reactions of the simpler dipolar ions, conclusions and inferences are drawn which are applied in the more complicated study of proteins themselves.

Proteins are highly specialized molecules in which certain general features of structure can be considered as established. Hemoglobin is an excellent example of the relation of specialized biologic function and protein structure. Knowledge of the specific adaptations of other proteins may be expected when the fields of study elaborated in this monograph are explored thoroughly.

Everyone interested in the physical chemistry of proteins will find this volume a necessity.

H. V.

VASCULAR SPASM: Experimental Studies. By ALEXANDER JOHN NEDZEL, M.D., M.S., Associate Professor of Pathology at the College of Medicine, University of Illinois, Chicago, Ill. Pp. 151; 161 figs. Urbana, Ill.: The University of Illinois Press, 1943. Price, \$2.75.

THIS monograph reviews the literature (with 300 references), and presents the results of an extended series of experiments on the general subject of vascular spasm with special reference to endocarditis, gastric ulcer, liver and kidneys, and multiple sclerosis. Pitressin was used intravenously to produce transient episodes of vasoconstriction in dogs. "Basic disturbances—spasms in vascular beds—appeared in different regions and organs in varying degrees, thus leading to the formation of lesions in widely separated organs. These lesions are bases for different diseases, and yet their etiology is the same." The author concludes that clinically those individuals with highly responsive and unstable vascular beds "have a disturbed splanchno-peripheral balance, their vascular rhythm is easily influenced, and the normal periods of increased tone are readily exaggerated or suppressed in the different regions and organs of the body." Thus the ultimate development of certain disease processes by essentially the same cause. His evidence for endocarditis is quite convincing, while that in the other organs is less impressive but reasonably suggestive. A large portion of the findings are shown in numerous microphotographs.

M. T.

NEUROSURGERY AND THORACIC SURGERY. Military Surgical Manuals, Vol. VI. Prepared and Edited by the Subcommittees on Neurosurgery and Thoracic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 310; many figs. Philadelphia: W. B. Saunders Company, 1943. Price, \$2.50.

PART I of this manual is designed primarily for medical officers who have had some training in neurosurgery; but the less specialized physician will find most of the information valuable and necessary in the evaluation of head, spinal cord, and peripheral nerve injuries, as well as certain infections involving the nervous system.

Part II deals with those aspects of thoracic surgery which are primarily the problems of advanced field and dressing stations. The fundamental mechanisms of physiopathology are stated clearly, and the basic principles of diagnosis and treatment are well defined.

No medical officer could be called adequately informed if he did not know most of the content in this manual, whether or not he is capable of acting in the capacity of neurosurgeon or thoracic surgeon. Civilian physicians and students will also find this to be an excellent review. The manual is written in outline form so that any subject can be readily reviewed within a few minutes.

T. T.

WAR INJURIES OF THE CHEST. Edited by H. MORRISTON DAVIES, M.A., M.D., M.Ch., F.R.C.S., and ROBERT COOPE, M.D., B.Sc., F.R.C.P. Pp. 131; 36 figs. Baltimore: Williams & Wilkins Company, 1942. Price, \$2.00.

THE stated object of this small book is "to give in concise form the reasons for and the details of the treatment of the various forms of chest injury met with in warfare." Although the reasons for treatment have been fairly well dealt with, the details have not been well expressed. For the physician who desires in an hour or two to gain a general concept of chest injuries and their management this should serve his purpose well.

T. T.

NEW BOOKS

Synopsis of Diseases of the Skin. By RICHARD L. SUTTON, M.D., Emeritus Professor of Dermatology, University of Kansas Medical School; and RICHARD L. SUTTON, JR., M.D., Assistant Professor of Dermatology, University of Kansas Medical School. Pp. 481; 413 illus. St. Louis: C. V. Mosby Company, 1942. Price, \$5.50.

The Embryological Treatises of Hieronymus Fabricius of Aquapendente. A facsimile edition, with an introduction, a translation, and a commentary by HOWARD B. ADELMANN, Professor of Histology and Embryology, Cornell University. Pp. 883; 85 figs. Ithaca, N. Y.: Cornell University Press, 1942. Price, \$12.00. Reviewed in this issue, p. 879.

Selection of Officer Candidates. 1. Studies in the Relation of Personality to Field of Work. From the Grant Study, Department of Hygiene, Harvard University, WILLIAM L. WOODS, M.D., LUCIEN BROUHA, M.D., CARL C. SELTZER, Ph.D. Pp. 46; 10 figs. Cambridge, Mass.: Harvard University Press, 1943. Price, 75 cents.

A short, concise communication with discussion, description and results of methods used and recommended for selection of officer candidates upon the basis of three inter-related tests: 1, physical fitness; 2, short interview; and, 3, "masculine component" evaluation. Charts, graphs and forms used in the method are also included. The monograph should be interesting to those selecting officer candidates.

H. H.

- Modern Trends in Ophthalmology.* Edited by FREDERICK RIDLEY and ARNOLD SORSBY. Pp. 699; 217 figs.; 8 color plates. First published in Great Britain, 1940. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1943. Price, \$10.00.
- Mind, Medicine, and Man.* By GREGORY ZILBOORG, M.D. Foreword by ARTHUR H. RUGGLES, M.D. Pp. 344. New York: Harcourt, Brace & Co., 1943. Price, \$3.50.
- Manual of Industrial Hygiene and Medical Service in War Industries.* Edited by WILLIAM M. GAFAFER, D.Sc. Issued under the auspices of the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council. Prepared by the Division of Industrial Hygiene, National Institute of Health, U. S. Public Health Service. A composite book with 16 distributors. Pp. 508; 20 illus. Philadelphia and London: W. B. Saunders Company, 1943. Price, \$3.00.

NEW EDITIONS

- Laboratory Experiments in Physiology.* By W. D. ZOETHOUT, Ph.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Third ed. Pp. 256; 88 illus. St. Louis: C. V. Mosby Company, 1943. Price, \$2.25.
- On Growth and Form.* By SIR D'ARCY WENTWORTH THOMPSON. Revised and enlarged ed. Pp. 1116; 554 figs. Cambridge: University Press. New York: The Macmillan Company, 1942. Price, \$12.50.
- Brucellosis in Man and Animals.* By I. FOREST HUDDLESON, D.V.M., M.S., Ph.D., Research Professor in Bacteriology, Michigan State College. Contributing Authors, A. V. HARDY, M.S., M.D., Dr.P.H., Associate Professor of Epidemiology, DeLamar Institute of Public Health, Columbia University Medical School, Consultant, U. S. Public Health Service; J. E. DEBONO, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta; WARD GILTNER, D.V.M., M.S., Dr.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Third ed. Pp. 379; 37 figs. New York: The Commonwealth Fund, 1943. Price, \$3.50.
- Text-book of Pathology.* By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), Dipl. Psych., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg, Canada. Fourth ed. Pp. 1008; 490 engravings (29 colored plates). Philadelphia: Lea & Febiger, 1943. Price, \$10.00.
- Neurology.* By ROY R. GRINKER, M.D., Chairman, The Department of Neuropsychiatry of the Michael Reese Hospital, Chicago. With the assistance of NORMAN A. LEVY, M.D., Associate Neuropsychiatrist, Michael Reese Hospital. Chapter on Brain Tumors by PAUL C. BUCY, M.D., Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago. Third ed. Pp. 1136; 416 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, \$6.50.
- Primer of Allergy.* By WARREN T. VAUGHAN, M.S., M.D., Richmond, Va. With illustrations by JOHN P. TILLERY. Second ed. Pp. 176. St. Louis: C. V. Mosby Company, 1943. Price, \$1.75.

This small volume continues to give the allergic patient a general understanding of the nature of allergic diseases in an interesting and delightful manner. It is especially appropriate in that most physicians are unable to take time to discuss in much detail the character of this disease and its management to their patients. The author is aware of the individuality of the practice of medicine, and has, likewise, presented his material with this in mind. This book is well recommended and should find a useful place in both the home and the reception room. M. T.

The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects.

By JOHN R. PAUL, M.D., Professor of Preventive Medicine, Yale University School of Medicine, and Other Contributors. Second ed. For the American Heart Assn. Pp. 163; various tables and figs. Printed by the Metropolitan Life Insurance Company. Copies will be sent without charge to physicians upon request. Address inquiries to the American Heart Assn., Inc., 1790 Broadway, New York.

Rheumatic fever, as one of the most important problems of heart disease—in fact, of internal medicine as a whole—has appropriately been the subject of many excellent studies in recent years. These have brought forth so much new information about the varied aspects of the disease since 1928, that again the American Heart Association has published this detailed statement on its epidemiology, the publication having again been made possible by a grant from the Metropolitan Life Insurance Company. Edited and largely composed by one who has himself contributed so much to this phase of the subject, it is the most authoritative statement available, and one that is a necessary tool for all progressive internists and public health specialists.

In this second edition, with a new title, Part I covers its Nomenclature, Definition, a Historical Review, and the relations of the disease to hemolytic streptococcus infection. In Part II, various epidemiological factors are discussed; and in Part III the Public Health aspects. Four appendices on techniques of study precede a list of some 318 recent references.

Though many copies of this edition have apparently already been distributed, a prompt inquiry addressed to the American Heart Association will probably not be in vain. E. K.

Blood Groups and Transfusion. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn, N. Y. Third ed. Pp. 438; 69 figs., 106 tables. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, \$7.50.

Notice to Contributors. Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we are changing the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a lesser number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, i. e., conservation of paper.

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